Die metastasierte Patientin
Therapieupdate
2019/2020

individuelle Auswahl

13.Brustkrebskongress

18.1.2020

I.Scheffen
St. Elisabeth Krankenhaus

Brustzentrum
Köln-Hohenlind

Financial Disclosures

- Vortragshonorare: Celgene, Novartis, Pfizer, Roche

- Honorierte Advisory-Board-Aktivitäten:

  MSD, Amgen, Roche, Novartis, Pfizer

- Teilnahme an klinischen Studien: keine

Metastatic breast cancer

Treatment strategies

Advanced breast cancer

- Supportive, palliative and psychosocial support from the onset
- Evaluate extent of disease, biopsy and assessment of ER and HER2 status

Luminal-like (ER+ and/or PR+, HER2-)

Triple negative (ER-, PR- and HER2-)

HER2+ (luminal-like or non-luminal-like)

Endocrine therapy with or without targeted therapy: multiple sequential lines are advised

•Premenopausal women: ovarian suppression or ablation plus another endocrine therapy

•All patients: Tamoxifen, an aromatase inhibitor or Fulvestrant in the first line or before

•CDK4/6 inhibitors plus endocrine therapy have good tolerance and improve PFS and overall survival in the first and second line

•Everolimus plus endocrine therapy improves PFS with acceptable toxicity (plus steroid mouthwashes) in the second line or beyond

If no more endocrine therapy-based options, rapid progression or visceral crisis

If germline *BRCA* mutations are present

PARP inhibitors

•Triple-negative: first line

•Luminal-like: after endocrine therapy

•Efficacy compared with Platinum is unknown

Chemotherapy

•If >1% PD-L1 immune cell staining, nab-Paclitaxel plus Atezolizumab is an option in the first line

•Platinum is a good option

•Other recommendations similar to luminal-like metastatic breast cancer

First line

Dual blockade (Trastuzumab and Pertuzumab) and chemotherapy (for example, Taxane or Vinorelbine)

Second line

T-DM1

Later lines

•Trastuzumab and chemotherapy

•Lapatinib and Trastuzumab

•Lapatinib and Capecitabine (less preferred)

Chemotherapy

•Use sequential monotherapy

•Preferred first-line agents for patients pretreated with Anthracycline and Taxane are Capecitabine, Vinorelbine or Eribulin

•Anthracycline or Taxane rechallenge possible (if ≥1 year from prior exposure)

•In combination with a Taxane or Capecitabine chemotherapy, Bevacizumab (an anti-VEGF antibody) is an option in the first line

•Many options are available for later lines, but the best sequence is unknown

Mod. Harbeck N et al., Nat Rev Dis Primers 9/2019;5(1):66

Therapie des metastasierten Mammakarzinoms

-HR+ Her2 negativ:

Behandlung mit CDK4/6 Inhibitoren **OS Daten** (3 Studien mit signifikanten OS benefit !!)

Young Pearl (Vergleich mit Chemotherapie erste Linie)

PIK3 Inhibitoreinsatz bei PIK3 Mutationsnachweis

Alpelisib (SOLAR-1),FDA Zulassung

-HR- Her 2 negativ

Immuntherapie (Impassion 130, Keynote 119)

PDL1-Testung

PARP-Inhibitoren → Spotlight Familiäres Mammakarzinom

-Her 2 positiv:

Monarch Her

Neue Substanzen (Margetuximab, Tucatinib, Drug-Konjugate) → Spotlight SABCS News 2019

-Ausblick in die Zukunft und „zurück zur Erde“ (Lokaltherapie)

Metastatic breast cancer

Treatment strategies

Advanced breast cancer

Luminal-like (ER+ and/or PR+, HER2-)

Endocrine therapy with or without targeted therapy: multiple sequential lines are advised

- Premenopausal women: ovarian suppression or ablation plus another endocrine therapy
- All patients: Tamoxifen, an aromatase inhibitor or Fulvestrant in the first line or before
- CDK4/6 inhibitors plus endocrine therapy have good tolerance and improve PFS and overall survival in the first and second line
- Everolimus plus endocrine therapy improves PFS with acceptable toxicity (plus steroid mouthwashes) in the second line or beyond

If no more endocrine therapy-based options, rapid progression or visceral crisis

If germline *BRCA* mutations are present

Vortrag Fr Dr. Herold

PARP inhibitors

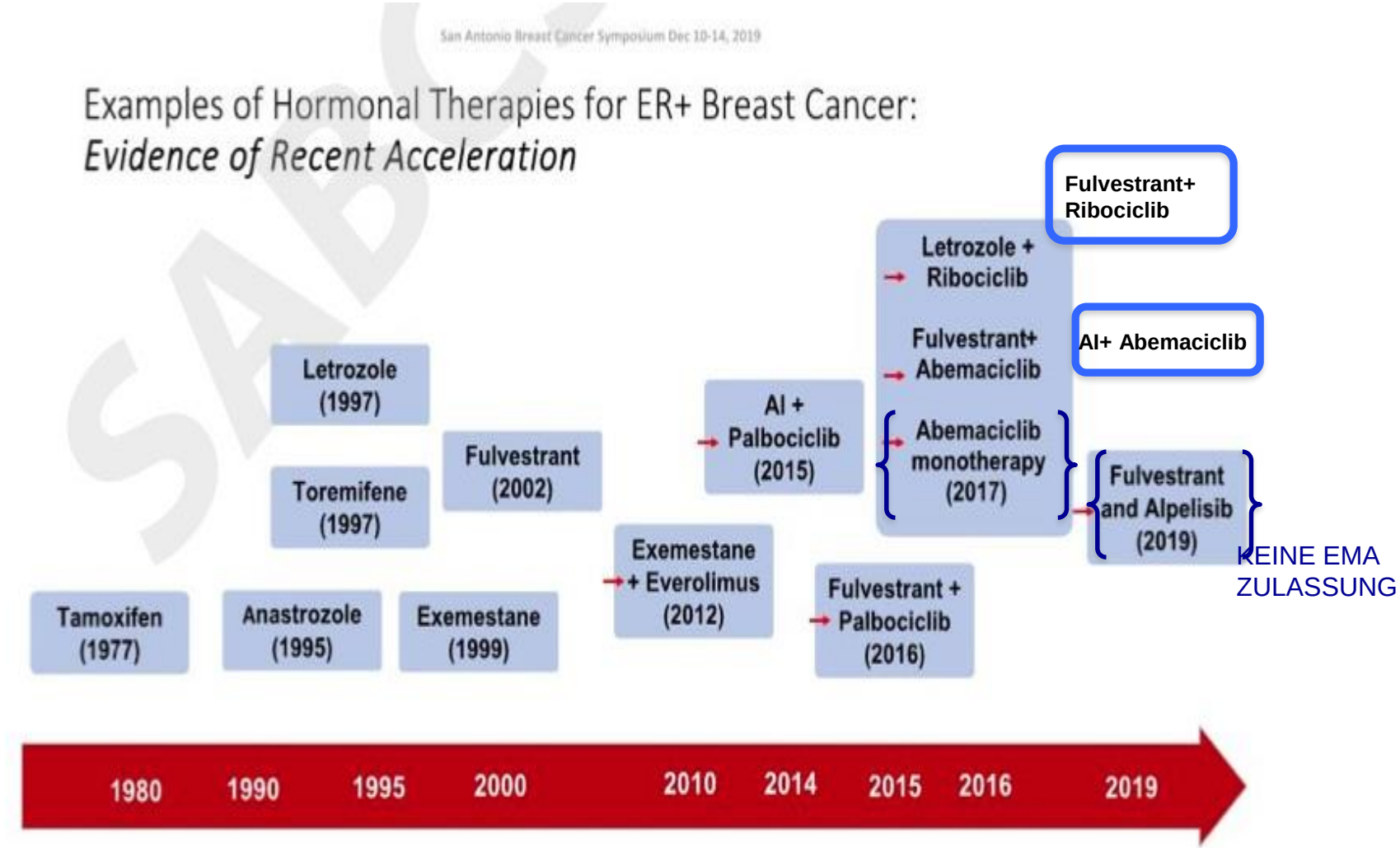
- Triple-negative: first line
- Luminal-like: after endocrine therapy
- Efficacy compared with Platinum is unknown

Chemotherapy

- Use sequential monotherapy
- Preferred first-line agents for patients pretreated with Anthracycline and Taxane are Capecitabine, Vinorelbine or Eribulin
- Anthracycline or Taxane rechallenge possible (if ≥1 year from prior exposure)
- In combination with a Taxane or Capecitabine chemotherapy, Bevacizumab (an anti-VEGF antibody) is an option in the first line
- Many options are available for later lines, but the best sequence is unknown

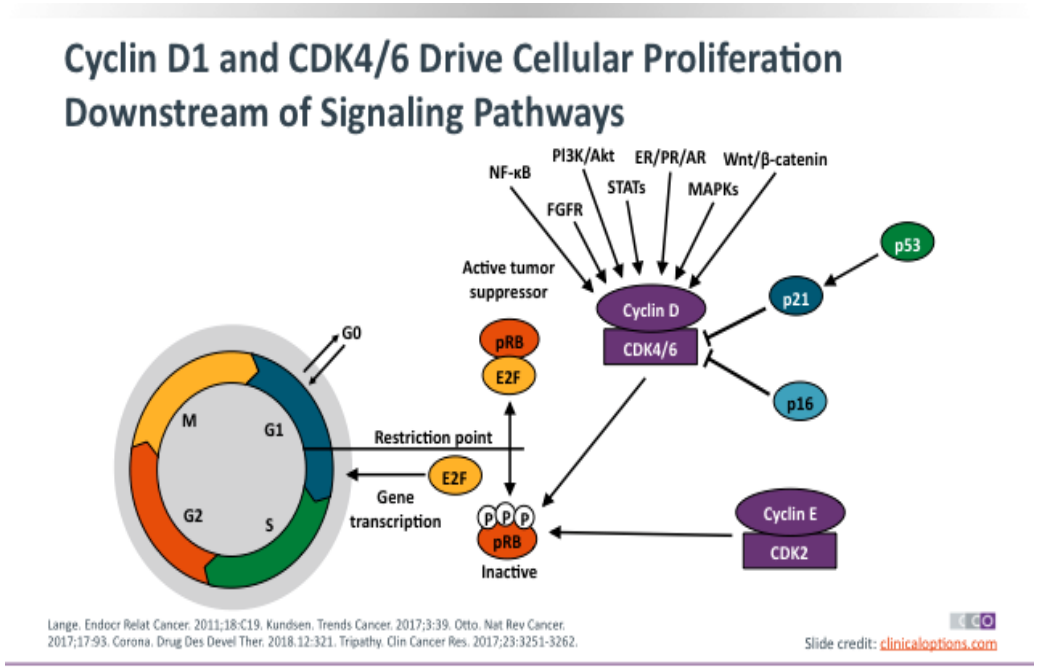
Mod. Harbeck N et al., Nat Rev Dis Primers 9/2019;5(1):66

Neue Therapieoptionen für das HR+ metastasierte Mammakarzinom



U.S. Food and Drug Administration. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Cyclin-Dependant Kinase 4/6 Inhibitoren
(Palbociclib, Ribociclib, Abemaciclib)



Impact of CDK4/6 Inhibition on PFS: First-Line Setting

Verdoppelung der Response Rate aller drei CDK4/6 Inhibitoren

	PALOMA-1[1]	PALOMA-2[2]	MONALEESA-2[3,4]	MONARCH-3[5]	MONALEESA-3[6]
Study design	Phase II 1st line	Phase III 1st line	Phase III 1st line	Phase III 1st line	Phase III 1st and 2nd line
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Patients, N	165	666	668	493	367
HR	0.49	0.58	0.56	0.54	0.57
PFS, mos	20.2 vs 10.2	24.8 vs 14.5	25.3 vs 16	NR vs 14.7	NR vs 18.3
ORR, %	56 vs 39	55.3 vs 44.4	52.7 vs 37.1	59 vs 44	40.9 vs 28.7*

*ORR includes 1st and 2nd line patients.

1. Finn. Lancet Oncol. 2015;16:25. 2. Finn. NEJM. 2016;375:1925. 3. Hortobagyi. NEJM. 2016;375:1738. 4. Hortobagyi. Ann Oncol. 2018;29:1541. 5. Goetz. J Clin Oncol. 2017;35:3638. 6. Slamon. J Clin Oncol. 2018;36:2465.

Impact of CDK4/6 Inhibition on PFS: Second-Line Setting

	PALOMA-3[1]	MONARCH-2[2]	MONALEESA-3[3]
Study design	Phase III 2nd Line	Phase III 2nd Line	Phase III 1st and 2nd line
Endocrine partner	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Abemaciclib	Ribociclib
Patients, N	521	669	346
HR	0.46	0.55	0.57
PFS, mos	9.5 vs 4.6	16.4 vs 9.3	14.6 vs 9.1
ORR, %	25 vs 11	48.1 vs 21.3	--

Different Patient Populations

Any # prior endocrine tx
1 prior chemo allowed

Only 1 prior endocrine tx
No prior chemo allowed

1. Cristofanilli. Lancet Oncol 2016;17:425. 2. Sledge. J Clin Oncol. 2017;35:2875. 3. Slamon. ESMO 2019. Abstr LBA7_PR.

Relatively High Objective Response Rates With CDK4/6 Inhibition

1st-Line Setting

	PALOMA-1[1]	PALOMA-2[2]	MONALEESA-2 [3]	MONA[illegible] [4]	MONALEESA-3 [5]
Study design	Phase II 1st line	Phase III 1st line	Phase III 1st line		Phase III 1st and 2nd line
CDK4/6i	Palbociclib	Palbociclib	[illegible]		Ribociclib
ORR, %	56 vs 39	55.3 vs 44.4			40.9 vs 28.7*

2nd-Line Setting and Beyond

	PA[illegible]	[illegible]	[illegible]NALEESA-3[8]	MONARCH-1[9]
Study design		[illegible]	Phase III 1st and 2nd line	Phase II Late line (1-2 prior CT)
CDK4/6 inhibitor	Pa[illegible]	[illegible]bemaciclib	Ribociclib	Abemaciclib
ORR, %	25 v[illegible]	48.1 vs 21.3	40.9 vs 28.7*	19.7

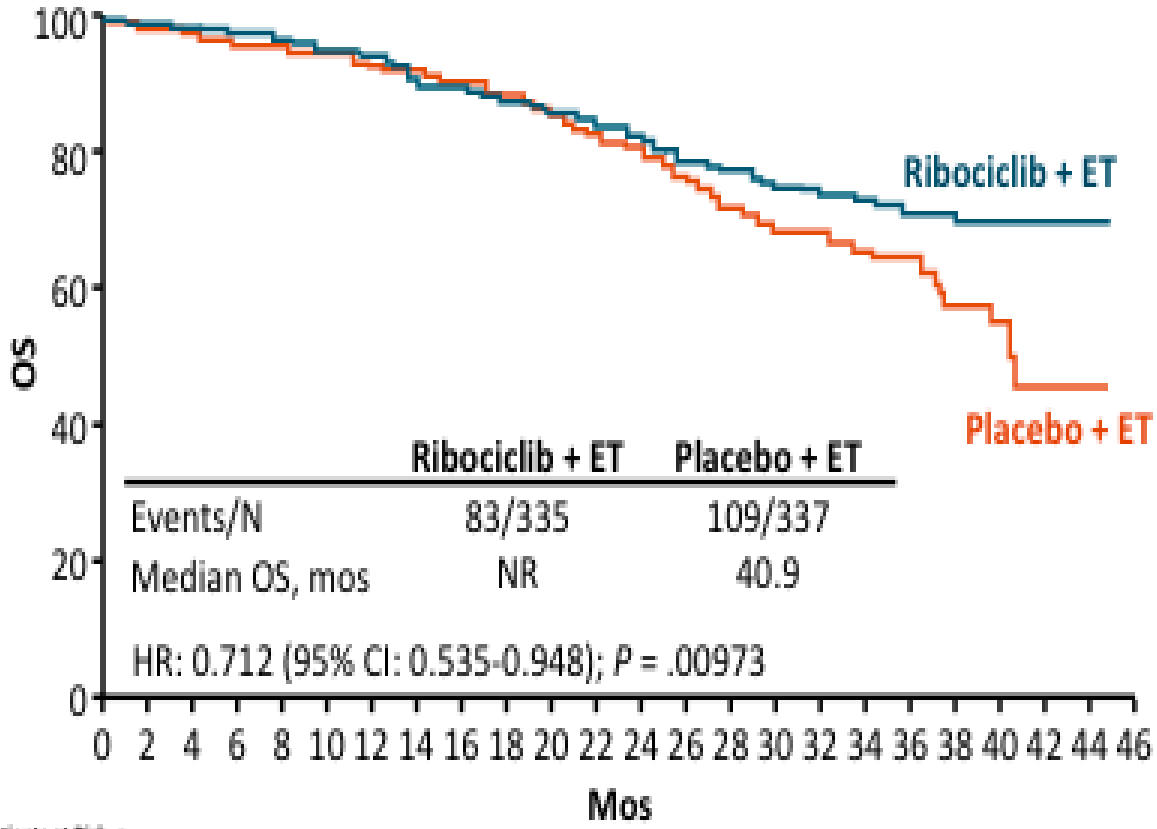
Verbessertes PFS gleich verbessertes OS ?

*ORR includes 1st and 2nd line patients.

1. Finn. Lancet Oncol. 2015;16:25. 2. Finn. NEJM. 2016;375:1925. 3. Hortobagyi. NEJM. 2016;375:1738. 4. Goetz. J Clin Oncol. 2017;35:3638. 5. Slamon. J Clin Oncol. 2018;36:2465. 6. Cristofanilli. Lancet Oncol 2016;17:425. 7. Sledge. J Clin Oncol. 2017;35:2875. 8. Slamon. ESMO 2019. Abstr LBA7_PR. 9. Dickler. Clin Cancer Res. 2017;23:5218.

Slide credit: clinicaloptions.com

MONALEESA-7: OS in All Patients (Key Secondary Endpoint)



Patients at Risk, n

Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	0

- 29% relative reduction in risk of death
- *P* value crossed the prespecified boundary for superior efficacy

Landmark Analysis, %	Ribociclib + ET	Placebo + ET
36-mo OS	71.9	64.9
42-mo OS	70.2	46.0

- Exploratory analyses observed generally consistent OS benefit across subgroups

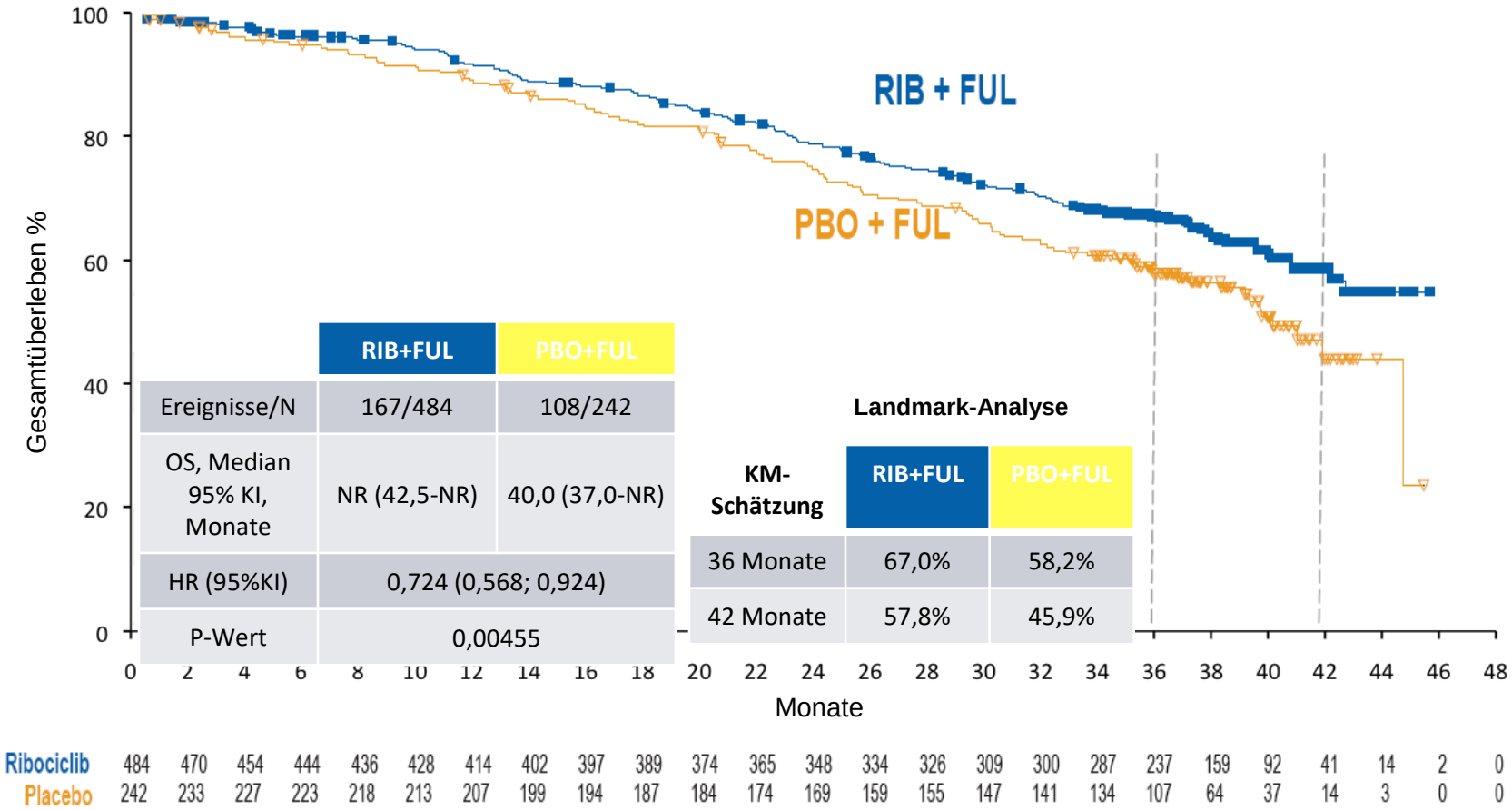
Hurvitz. ASCO 2019. Abstr LBA1008. Im. NEJM. 2019;[Epub].

Slide credit: clinicaloptions.com

MONALEESA-3

OS: Reduktion des relativen Todesrisikos um 28% im Ribociclib-Arm

Der P-Wert lag mit 0,00455 im präspezifizierten Bereich für den Nachweis der Überlegenheit (P<0,01129).



	RIB+FUL	PBO+FUL
Ereignisse/N	167/484	108/242
OS, Median 95% KI, Monate	NR (42,5-NR)	40,0 (37,0-NR)
HR (95%KI)	0,724 (0,568; 0,924)	
P-Wert	0,00455	

Landmark-Analyse

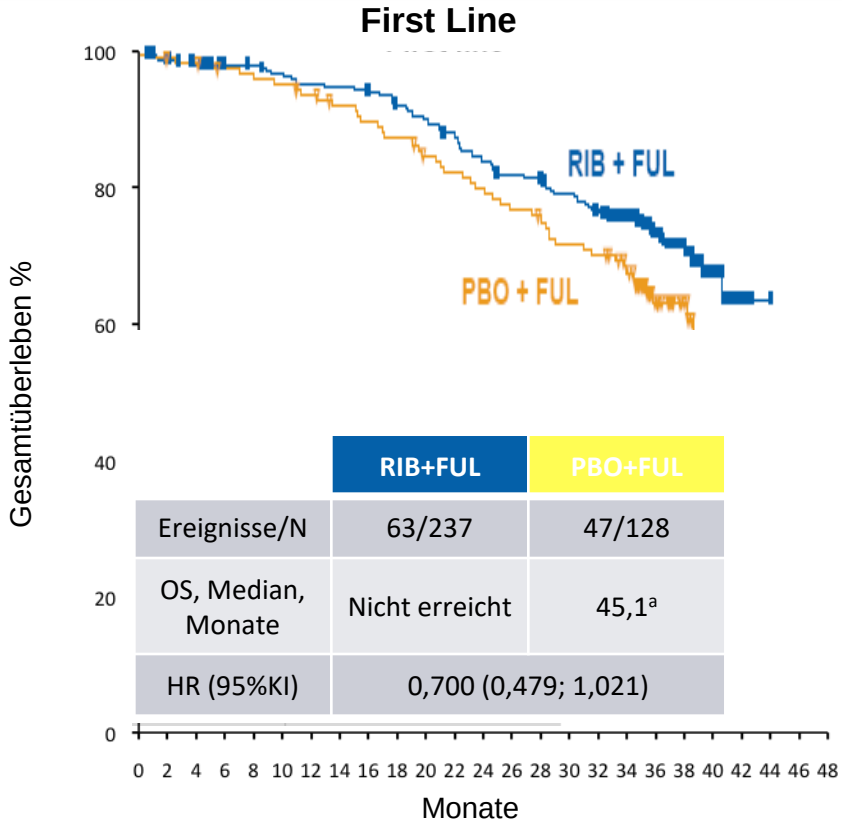
KM-Schätzung	RIB+FUL	PBO+FUL
36 Monate	67,0%	58,2%
42 Monate	57,8%	45,9%

NR: nicht erreicht

Slamon et al. | 2019 ESMO Annual Meeting | LBA7_PR

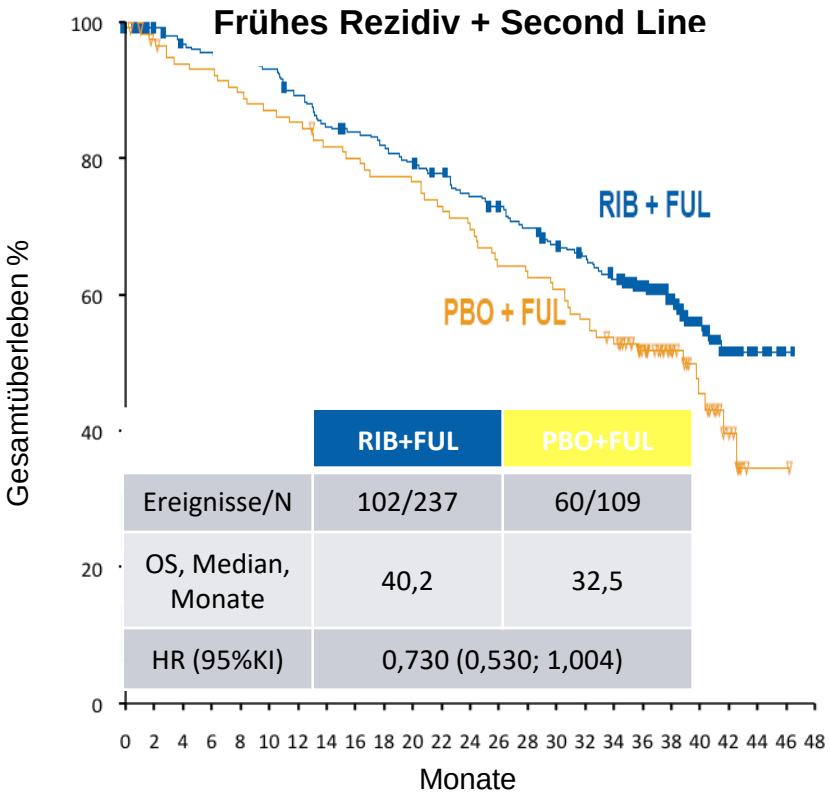
MONALEESA-3

OS: Gesamtüberleben nach Therapielinien war konsistent zur Gesamtpopulation



	RIB+FUL	PBO+FUL
Ereignisse/N	63/237	47/128
OS, Median, Monate	Nicht erreicht	45,1[a]
HR (95%KI)	0,700 (0,479; 1,021)	

Ribociclib 237 229 222 217 214 210 207 206 205 202 194 190 182 174 173 166 163 157 138 92 54 22 6 1 0
Placebo 128 126 125 122 121 119 116 113 110 106 104 99 97 93 91 85 84 82 70 40 21 8 2 0 0



	RIB+FUL	PBO+FUL
Ereignisse/N	102/237	60/109
OS, Median, Monate	40,2	32,5
HR (95%KI)	0,730 (0,530; 1,004)	

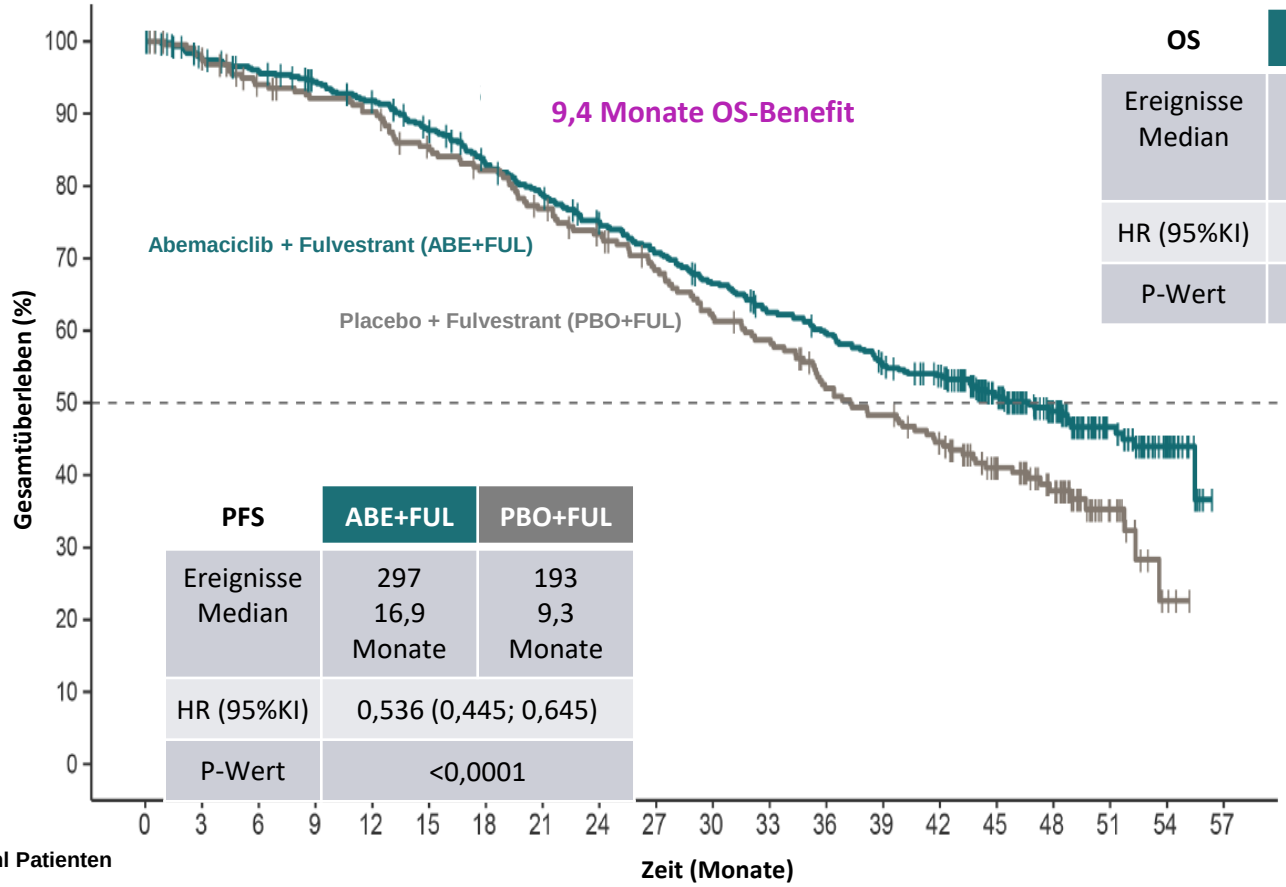
Ribociclib 237 231 222 218 213 210 199 188 184 179 172 167 158 152 145 135 129 122 94 63 36 17 7 1 0
Placebo 109 103 98 97 93 90 88 83 81 78 77 72 69 63 61 59 54 49 35 23 15 6 1 0 0

[a]Die Schätzung des medianen Wertes ist evtl. nicht glaubwürdig, da der letzte Patient im Follow-Up nach 45,1 Monaten ein Ereignis hatte.

Slamon et al. | 2019 ESMO Annual Meeting | LBA7_PR

MONARCH 2

Gesamtüberleben (OS)



OS	ABE+FUL	PBO+FUL
Ereignisse Median	211 46,7 Monate	127 37,3 Monate
HR (95%KI)	0,757 (0,606; 0,945)	
P-Wert	0,0137	

PFS	ABE+FUL	PBO+FUL
Ereignisse Median	297 16,9 Monate	193 9,3 Monate
HR (95%KI)	0,536 (0,445; 0,645)	
P-Wert	<0,0001	

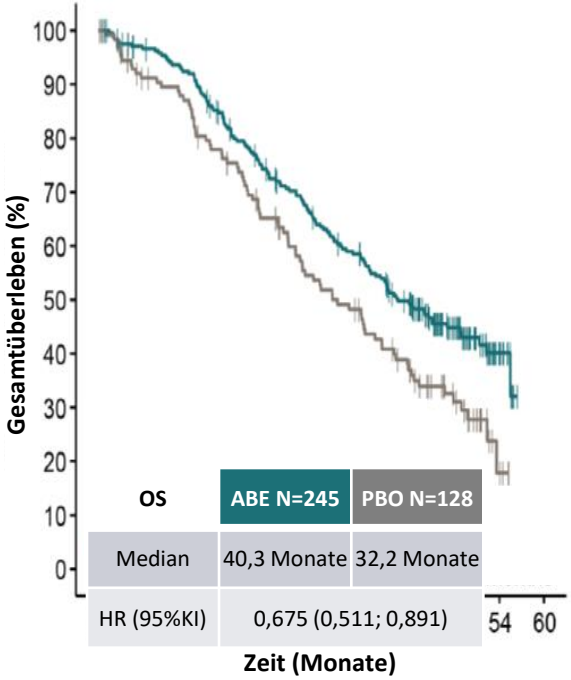
Anzahl Patienten	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Abemaciclib + Fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
Placebo + Fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

Sledge et al. | 2019 ESMO Annual Meeting | LBA6

MONARCH 2

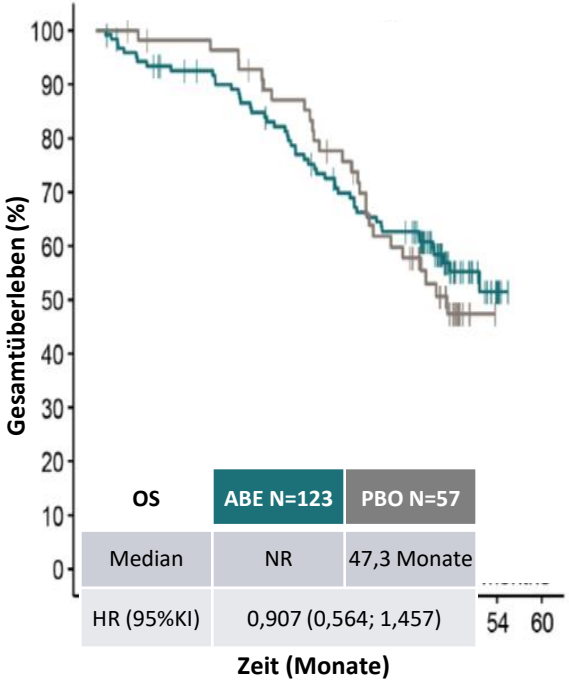
Gesamtüberleben nach Metastasen-Lokalisation

Viszeral



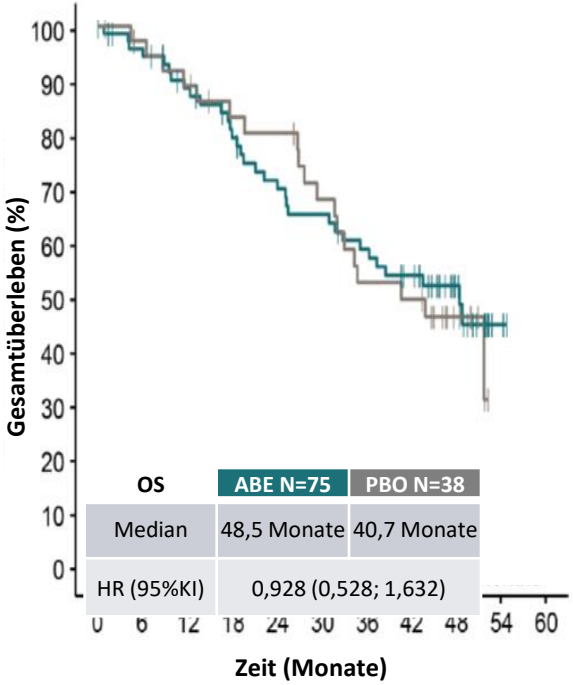
OS	ABE N=245	PBO N=128
Median	40,3 Monate	32,2 Monate
HR (95%KI)	0,675 (0,511; 0,891)	

Ausschließlich Knochen



OS	ABE N=123	PBO N=57
Median	NR	47,3 Monate
HR (95%KI)	0,907 (0,564; 1,457)	

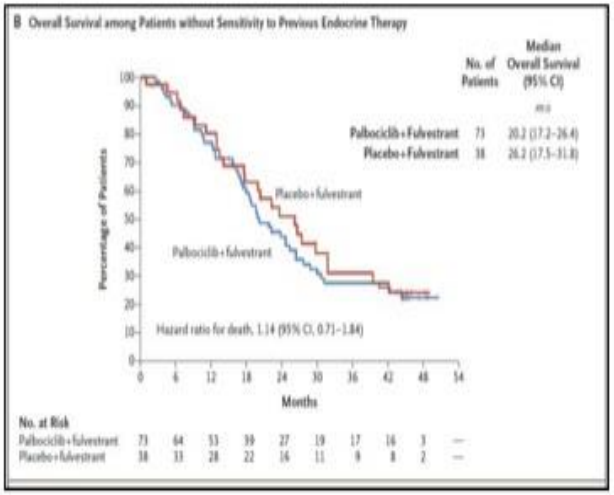
Andere Metastasen

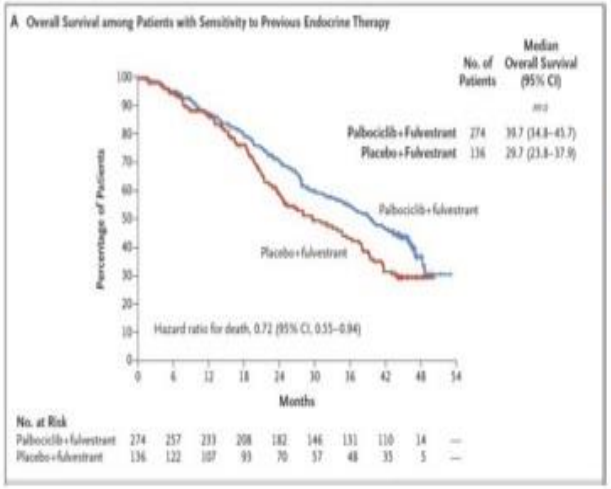


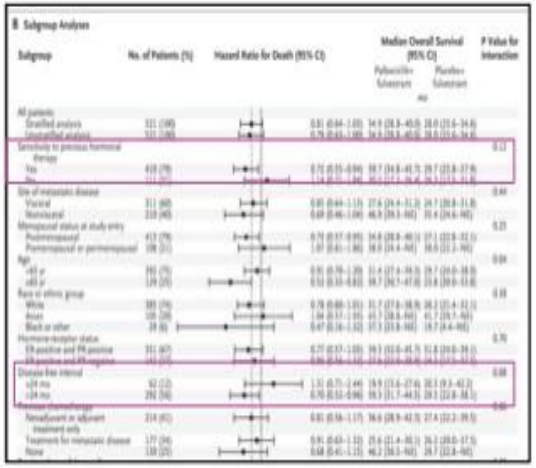
OS	ABE N=75	PBO N=38
Median	48,5 Monate	40,7 Monate
HR (95%KI)	0,928 (0,528; 1,632)	

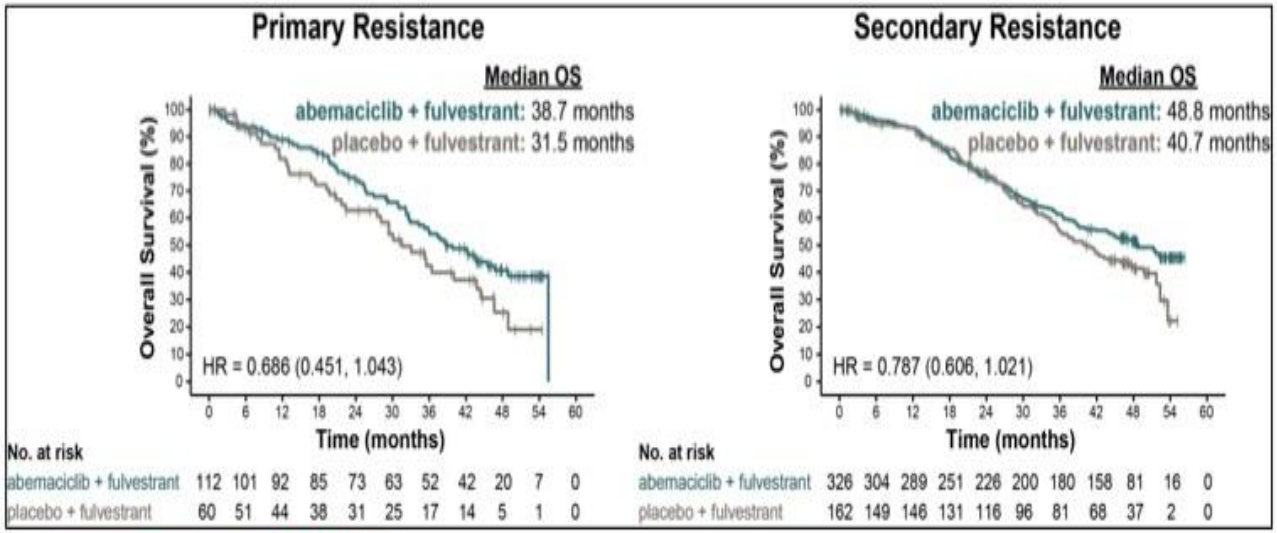
Sledge et al. | 2019 ESMO Annual Meeting | LBA6

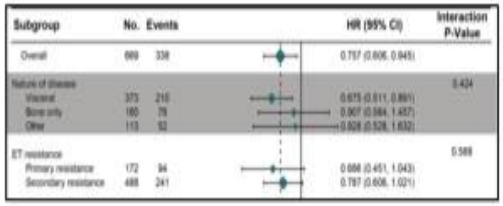
Results for Sensitive vs Non-Sensitive in PALOMA-3 and MONARCH 2











Endocrine Resistance (ESMO guidelines)

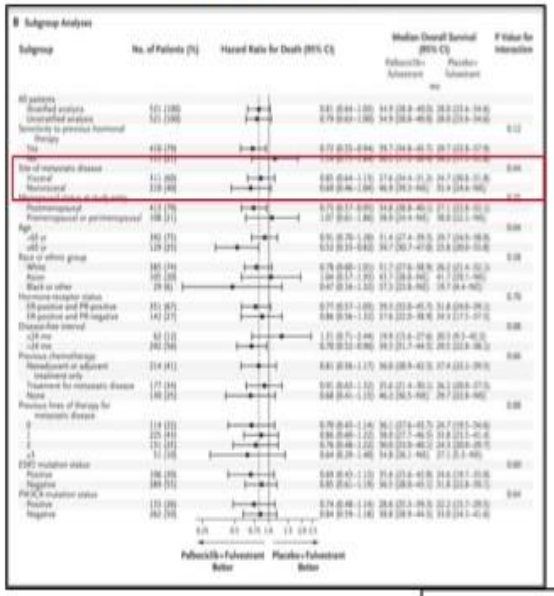
- **Primary:** relapse while on the **first 2 years of adjuvant ET**, or PD **within first 6 months of 1st line ET** for MBC, while on ET
- **Secondary**: relapse while on adjuvant ET but after the first 2 years, or Relapse within 12 months of completing adjuvant ET, or PD 6 months after initiating ET for MBC, while on ET

BARCELONA 2019 ESMO congress

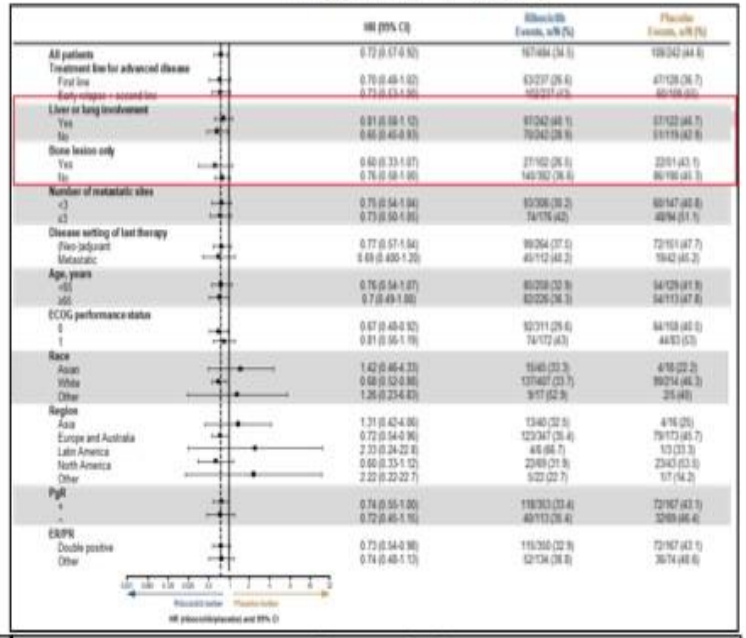
Turner N et al. New Engl J 2018; Sledge G et al. ESMO 2019 LBA

Overall Survival by Metastatic Site

PALOMA 3



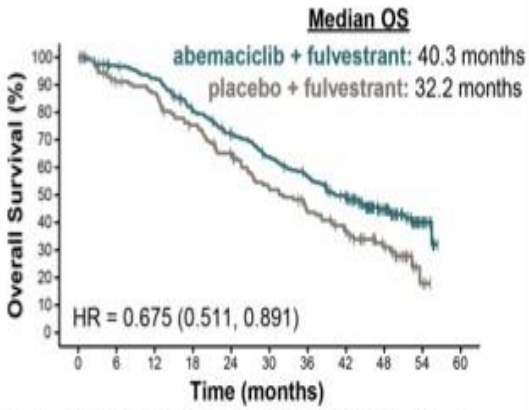
MONALEESA 3



MONARCH 2

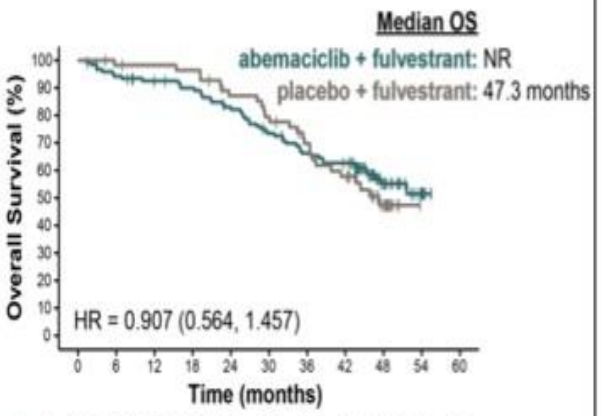
Subgroup	No.	Events	HR (95% CI)	Interaction P-Value
Overall	669	338	0.757 (0.608, 0.945)	
Nature of disease				0.424
Visceral	373	210	0.675 (0.511, 0.891)	
Bone only	180	76	0.907 (0.564, 1.457)	
Other	113	52	0.828 (0.528, 1.602)	
ET resistance				0.588
Primary resistance	172	94	0.886 (0.451, 1.043)	
Secondary resistance	488	241	0.797 (0.608, 1.021)	

Visceral



No. at risk											
abemaciclib + fulvestrant	245	228	217	184	162	141	124	102	57	13	0
placebo + fulvestrant	128	111	105	89	75	58	47	37	21	3	0

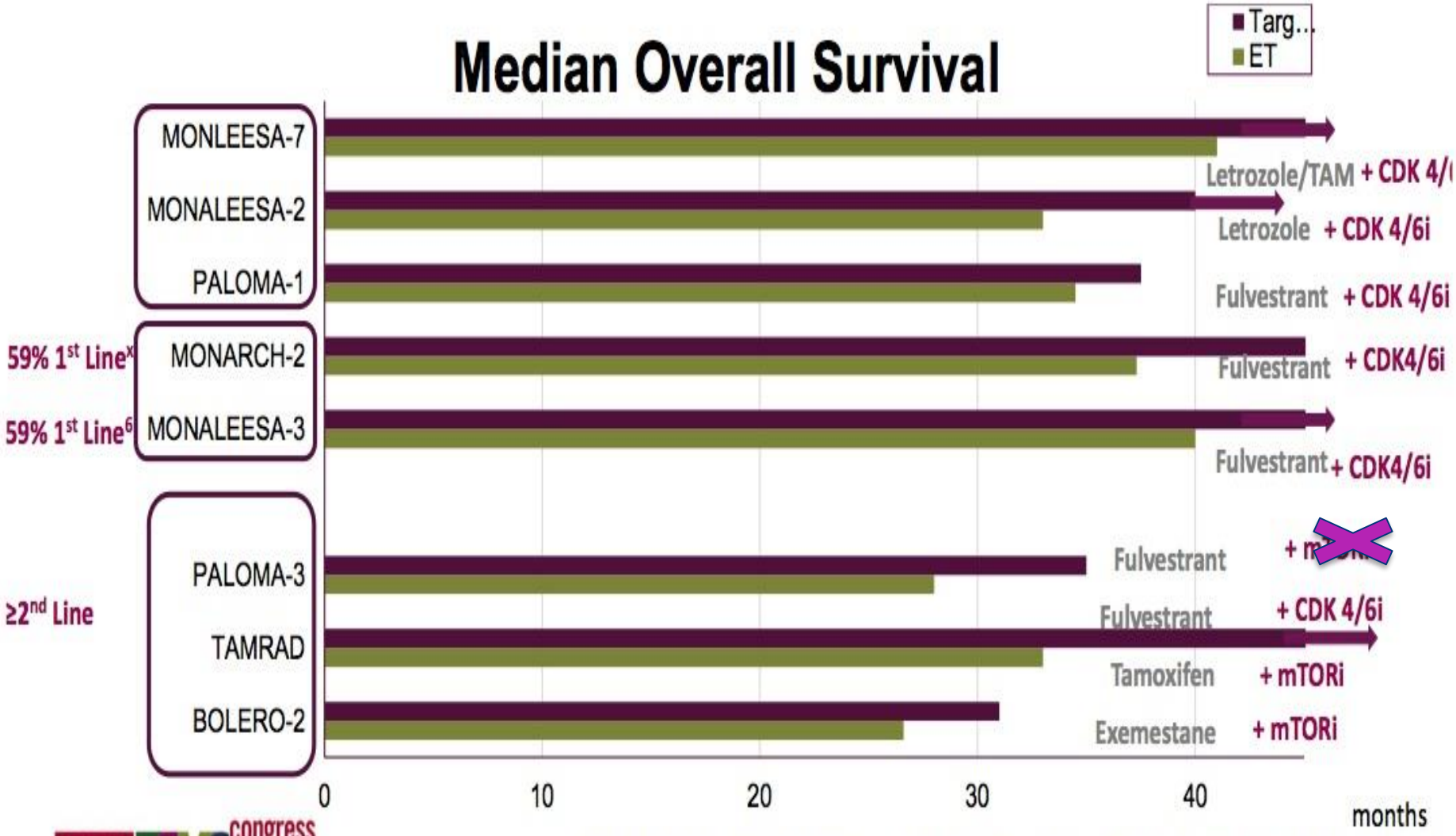
Bone Only



No. at risk											
abemaciclib + fulvestrant	123	114	108	104	95	83	74	69	28	8	0
placebo + fulvestrant	57	55	54	53	46	42	35	29	14	0	0

Effect of Targeted Agents on the Backbone Endocrine Therapy

Results of Clinical Trials in HR+, HER2– ABC



BARCELONA 2019 ESMO congress

Im SA, et al. New Engl J Med 2019; Hortobagyi GN, et al. ASCO 2017. Abstract 1038 [poster]; . Finn RS, et al. *Lancet Oncol.* 2015;16(1):25-352. and ASCO 2017 oral; Turner NC, et al. *New Eng J Med.* 2015;373(3):209-220; Bachelot T, et al. *J Clin Oncol.* 2012;30:2718-2724; Piccart M et al ,J Clin Oncol 2012.

Zusammenfassung

- Die einzelnen Studien können und sollten nicht miteinander verglichen werden! (verschiedene Studienpopulationen und Subgruppen)
- CDK4/6 Inhibitoren zeigen ein **PFS in der ersten und zweiten Linie** beim mBC mit nachweislicher Übersetzung **in drei Studien in ein OS** !!!
- Verbessertes Outcome war insgesamt **unabhängig** von der Vorbehandlung, dem Menopausenstatus, der endokrinen Sensitivität und der Metastasenlokalisation
- Bisher **keine Biomarker**, die eine Subgruppenanalyse für mehr oder weniger klinischen benefit identifizieren

Phase 3 CDK4/6 inhibitor clinical trials in HR+, HER2– ABC unterschiedliche Subgruppen

	MONALEESA-2[1] (N = 668)	MONALEESA-3[2] (N = 726)	MONALEESA-7[3] (N = 672)	MONARCH-2[4] (N = 669)	MONARCH-3[5] (N = 493)	PALOMA-2[6] (N = 666)	PALOMA-3[7] (N = 521)
Patient population	Postmenopausal women	Men and postmenopausal women[a]	Premenopausal women	Pre- and postmenopausal women	Postmenopausal women	Postmenopausal women	Pre- or postmenopausal women
Prior therapy	Previous (neo)adjuvant ET and CT allowed No prior ET or CT for ABC	Previous (neo)adjuvant ET and CT allowed Previous ET for ABC allowed (≤ 1L) No prior CT for ABC	Previous (neo)adjuvant ET and CT allowed Previous CT for ABC allowed (≤ 1L) No prior ET for ABC	Previous (neo)adjuvant ET and CT allowed Previous ET for ABC allowed (≤ 1L) No prior CT for ABC	Previous (neo)adjuvant ET and CT allowed No prior ET or CT for ABC	Previous (neo)adjuvant ET and CT allowed No prior ET or CT for ABC	Previous adjuvant ET and (neo)adjuvant CT allowed Previous ET for ABC allowed Previous CT for ABC allowed (≤ 1L)
Treatment arm	RIBO + LET (n = 334)	RIBO + FUL (n = 484)	RIBO + ET + GOS (n = 335)	ABE + FUL (n = 446)	ABE + NSAI (n = 328)	PAL + LET (n = 444)	PAL + FUL (n = 347)

METAANALYSE ?

[a] Although male patients were eligible for enrollment after a protocol amendment, because of rapid recruitment, no male patients were enrolled.
Not intended for cross-comparison.
1L, first line; ABC, advanced breast cancer; ABE, abemaciclib; CT, chemotherapy; ET, endocrine therapy; FUL, fulvestrant; GOS, goserelin; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; PAL, palbociclib; RIBO, ribociclib.

1. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547; 2. Slamon DJ, et al. *J Clin Oncol*. 2018;36(24):2465-2472; 3. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; 4. Sledge GW, et al. *J Clin Oncol*. 2017;35(25):2875-2884; 5. Goetz MP, et al. *J Clin Oncol*. 2017;35(32):3638-3646; 6. Finn RS, et al. *N Engl J Med*. 2016;375(20):1925-1936; 7. Turner NC, et al. *N Engl J Med*. 2015;373(3):209-219.

BEYOND PROGRESS ?

Bis jetzt Nein

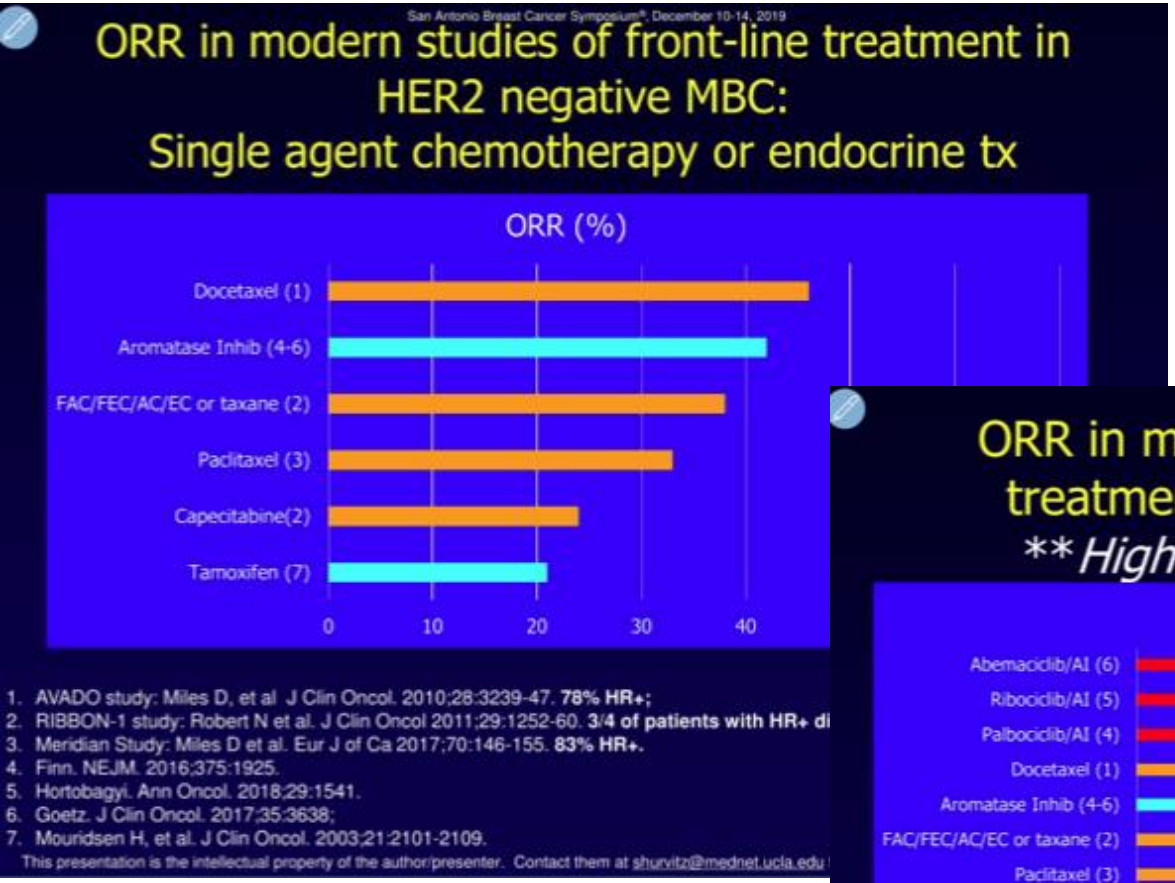
WAS DÜRFEN WIR ERWARTEN??

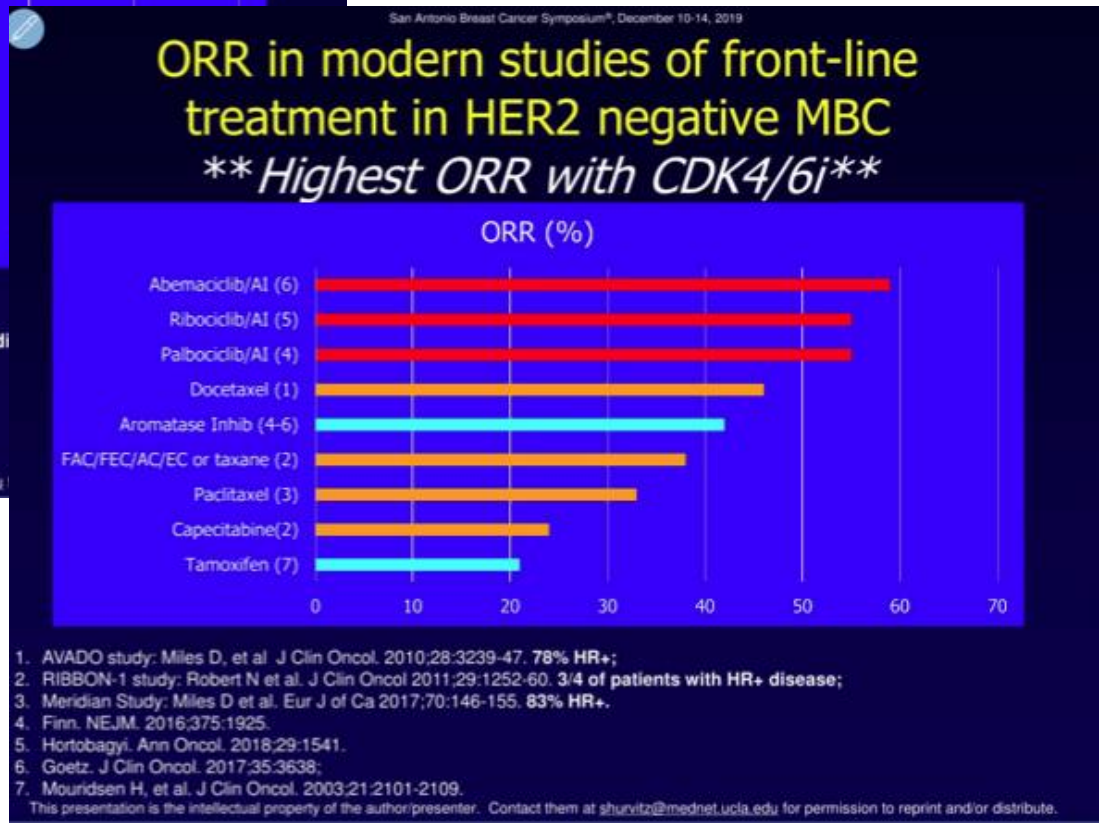
Trial	Agent	Setting	Phase	N	Endpoint	Study Design
MAINTAIN[1]	Ribociclib	HR+/HER2- locally advanced or MBC following progression on a CDK4/6 inhibitor	II	132	PFS at WK 24	Fulvestrant + ribociclib vs fulvestrant + placebo
PACE[2]	Palbociclib	Endocrine pre-treated ER+/HER2- MBC; after CDK and endocrine therapy	II	220	PFS	Fulvestrant vs fulvestrant + palbociclib vs fulvestrant + palbociclib + avelumab
TRINITI-1[3]	Ribociclib + everolimus	HR+/HER2- locally advanced or MBC following progression on a CDK4/6 inhibitor	I/II	107	Phase 1: MTD Phase 2: CBR	Ribociclib + everolimus + exemestane

1. NCT02632045. 2. NCT03147287. 3. NCT02732119.

Slide credit: clinicaloptions.com

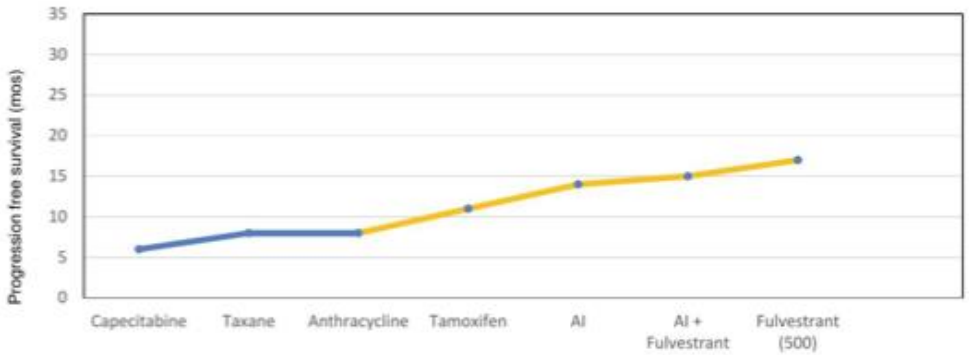
GIBT ES „NOCH“ EINE INDIKATION ZUR CHEMOTHERAPIE FIRST LINE BEIM HR+/HER2- MAMMAKARZINOM ?





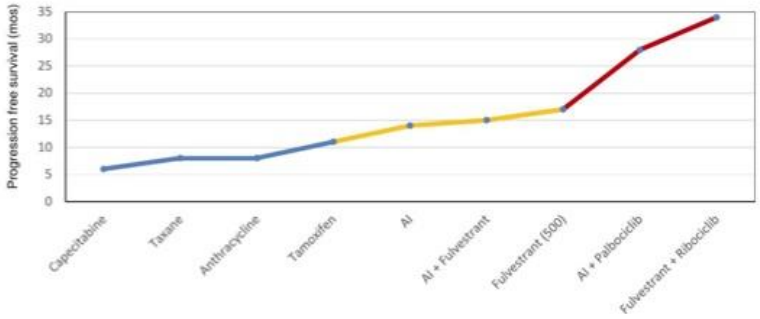
GIBT ES „NOCH“ EINE INDIKATION ZUR CHEMOTHERAPIE FIRST LINE BEIM HR+/HER2- MAMMAKARZINOM ?

PFS in modern studies of HER2-/HR+ MBC: Endocrine therapy outperforms chemo



RIBBON-1 (capecitabine, taxane, anthracycline): Robert N et al. J Clin Oncol 2011;29:1252-60. MONALEESA-7 (tamoxife and AI): Tripathy D et al. Lancet Oncol. 2018. SWOG-022
fulvestrant): Mehta R et al. N Engl J Med 2012;367:435-44. FALCON (Fulvestrant, AI) Robertson J et al. Lancet Oncol. 2016;388:2997-3005.

Highest PFS ever reported for 1st line HER2-/HR+ MBC is with CDK4/6i-based therapy

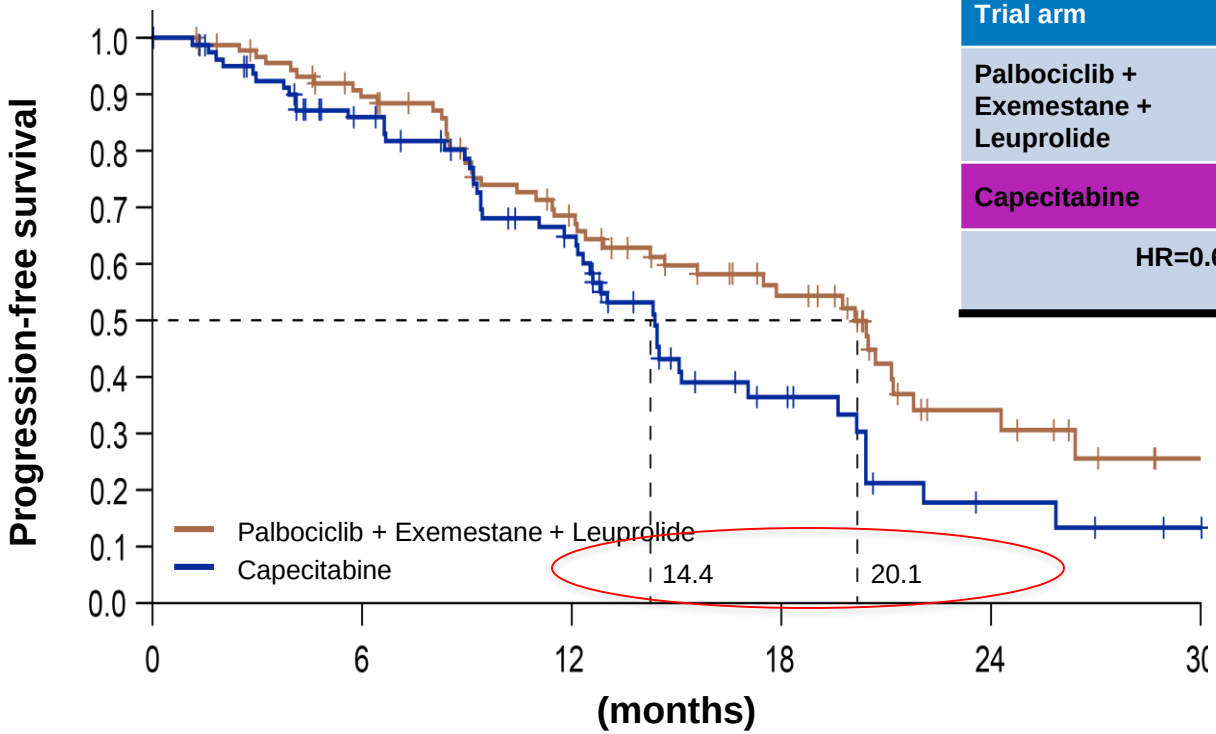


RIBBON-1 (capecitabine, taxane, anthracycline): Robert N et al. J Clin Oncol 2011;29:1252-60. MONALEESA-7 (tamoxife and AI): Tripathy D et al. Lancet Oncol. 2018. SWOG (AI + fulvestrant): Mehta R et al. N Engl J Med 2012;367:435-44. FALCON (Fulvestrant, AI) Robertson J et al. Lancet Oncol. 2016;388:2997-3005. PALOMA-2 (AI+palbociclib) Rugo H et al. Breast Cancer Res Treat 2019;174:719-29. MONALEESA-3 (fulvestrant/ribociclib, first line subgroup) Slamon DJ et al. ESMO 2019

Young-PEARL – Results

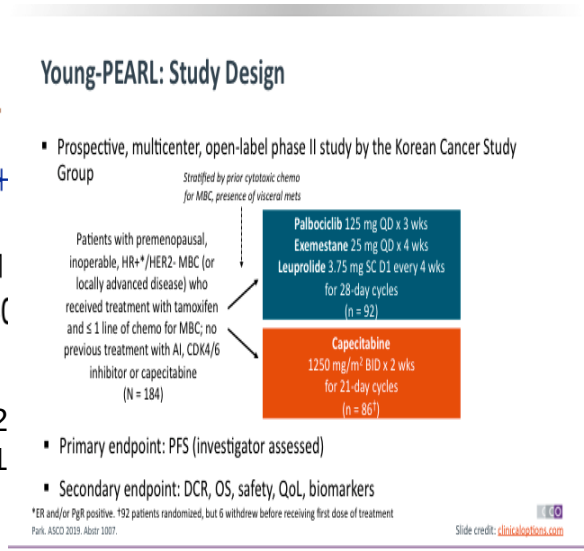
Investigator-assessed progression-free survival

Enrolment: Jun 2015 – Sep 2018; Data cut-off: Feb 1, 2019; Median follow-up duration: 17 months.



Arm A	92	89	85	82	74	59	49	38	28	16	10	5	2
Arm B	83	81	73	65	61	52	40	20	14	6	4	2	1

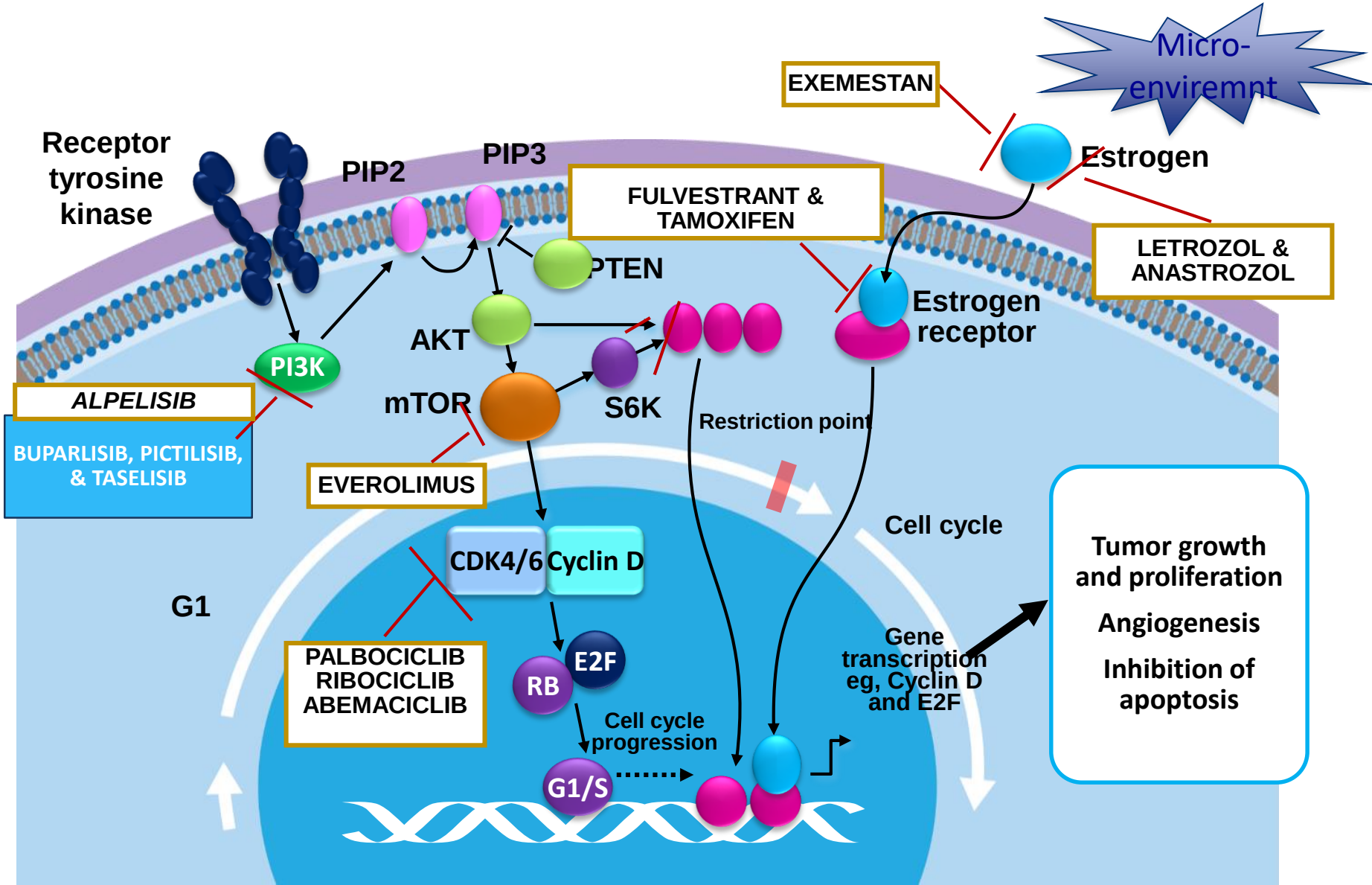
Trial arm	Events	Median	95% CI
Palbociclib + Exemestane + Leuprolide	44	20.1	14.2–21.8
Capecitabine	47	14.4	12.1–17.0
HR=0.659 (95% CI 0.437–0.994) p=0.0469			



22% Chemo in der metastasierten Situation
48% 1-2 Therapielinien in mBC
86% Tamoxifenresistenz

Mod. Park HY et al. ASCO 2019, Oral Abstract Session – Breast Cancer – Metastatic, Abstract No. 1007

Targets des HR+, Her2 – metastasierten Mammakarzinoms



Development of PI3K Inhibitoren in Solid Tumors[1,2]

PAN-PI3K

Buparlisib

Copanlisib

Pictilisib

Pilaralisib

DUAL PAN-PI3K/mTOR

Apitolisib

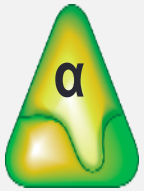
BEZ235

Gedatolisib

GSK2126458

ISOFORM SPECIFIC

Alpelisib (α)



mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PI3Ki, PI3K inhibitor.

1. Janku F. *Cancer Treat Rev.* 2017;59:93-101; 2. NCT03006172.

SOLAR-1 Study Design

A Phase 3 Randomized, Controlled Trial of Alpelisib + Fulvestrant in HR+, HER2– ABC

Men or postmenopausal women, with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

(N=572)

PIK3CA-mutant cohort (n=341) → R →
- **ALP** 300 mg QD PO + **FUL** 500 mg IM[a] **n=169**
- **PBO** + **FUL** 500 mg IM[a] **n=172**

1:1, stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

PIK3CA-non-mutant cohort (n=231) → R →
- **ALP** 300 mg QD PO + **FUL** 500 mg IM[a] **n=115**
- **PBO** + **FUL** 500 mg IM[a] **n=116**

Primary endpoint

PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include:

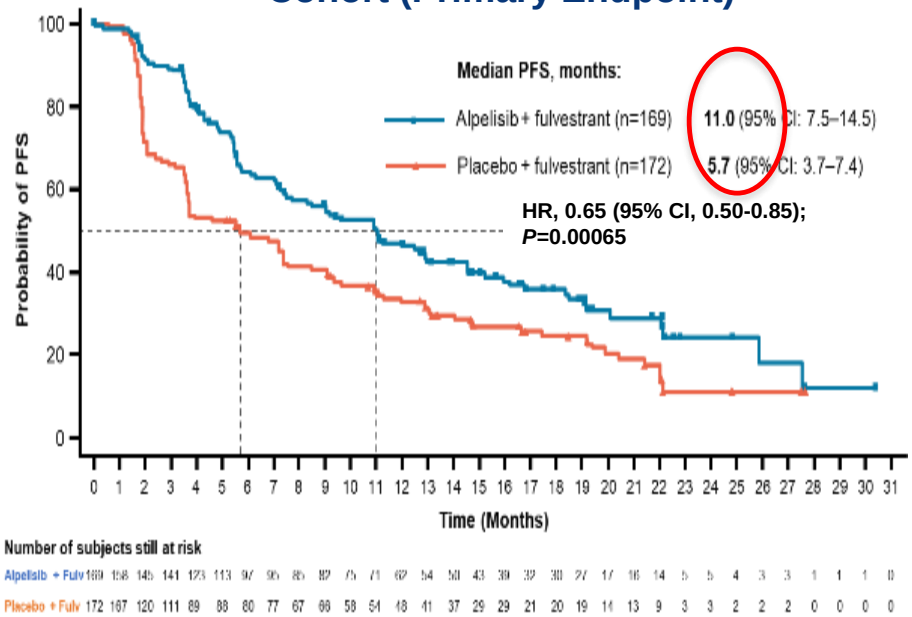
- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- OS (*PIK3CA*-non-mutant cohort)
- ORR/CBR
- Safety

[a] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28 day cycles.
Reprinted from Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

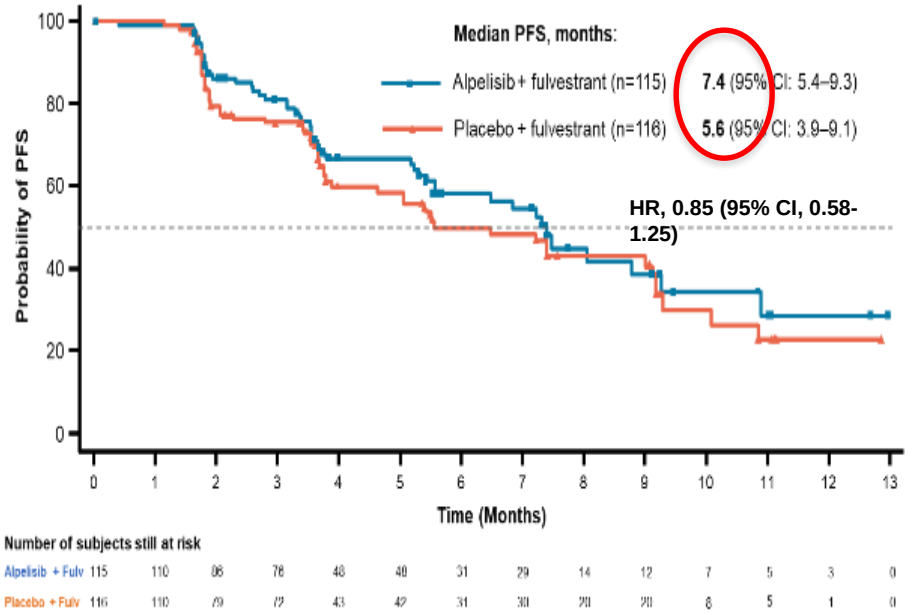
SOLAR-1 PFS

Locally Assessed PFS in the PIK3CA-*Mutant and Non-Mutant Cohorts*

PFS in the *PIK3CA*-Mutant Cohort (Primary Endpoint)



PFS in the *PIK3CA*–Non-Mutant Cohort

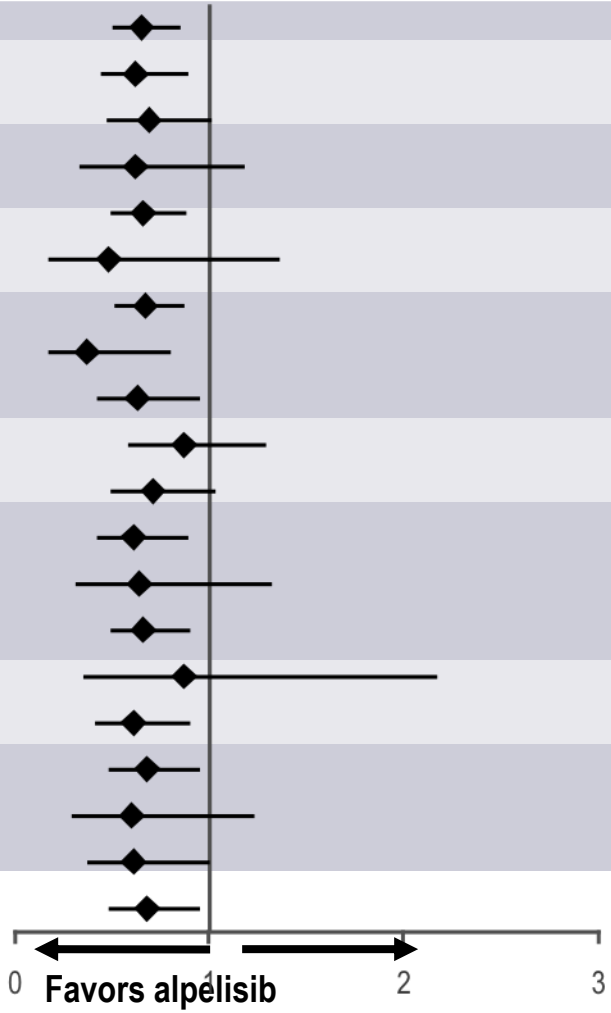


- **In SOLAR-1, data suggest that *PIK3CA* is a predictive biomarker for alpelisib clinical activity**

For the *PIK3CA*-mutant cohort, the primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided $P \leq 0.0199$).
For the non-mutant cohort: proof of concept criteria, estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1.
Reprinted from Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

PFS by Subgroup in SOLAR-1 (*PIK3CA*-Mutant Cohort)

Subgroup		No. of patients	Hazard Ratio (95% CI)
All subjects		341	0.65 (0.50–0.85)
Lung/liver metastases	Yes	170	0.62 (0.44–0.89)
	No	171	0.69 (0.47–1.01)
Bone-only disease	Yes	77	0.62 (0.33–1.18)
	No	264	0.66 (0.49–0.88)
Prior CDK4/6 inhibitor treatment	Yes	20	0.48 (0.17–1.36)
	No	321	0.67 (0.51–0.87)
Prior chemotherapy	Neoadjuvant	46	0.37 (0.17–0.80)
	Adjuvant	161	0.63 (0.42–0.95)
	None	133	0.87 (0.58–1.29)
Line of advanced anti-cancer treatment	First line	177	0.71 (0.49–1.03)
	Second line	161	0.61 (0.42–0.89)
Endocrine status	Primary resistance	45	0.64 (0.31–1.32)
	Secondary resistance	247	0.66 (0.49–0.90)
	Sensitive	39	0.87 (0.35–2.17)
PIK3CA mutation exon	Exon 9	165	0.61 (0.41–0.90)
	Exon 20	193	0.68 (0.48–0.95)
PIK3CA mutation subtype[a]	*E542K*	60	0.60 (0.29–1.23)
	E545X[b]	105	0.61 (0.37–1.00)
	H1047X[b]	193	0.68 (0.48–0.95)



[a] Mutations detected in tissue. Patients may have had more than one *PIK3CA* mutation.
[b] Includes multiple subtypes of *E545* and *H1047*.

Reprinted from Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Adverse Events in the Total Population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant (n=284)			Placebo + fulvestrant (n=287)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash[a]	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- Overall, 18 patients (6.3%) discontinued alpelisib treatment due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Any-grade and grade 3 maculopapular rash was observed in, respectively, 14.1% and 8.8% of patients in the alpelisib arm, vs 1.7% and 0.3% in the placebo arm

[a] Single preferred term of “rash” does not include preferred term of “maculopapular rash.”

Reprinted from Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Zusammenfassung der Studienergebnisse

- Alpelisib + Fulvestrant ist eine potentiell neue Therapieoption für PatientInnen mit nachgewiesener PIK3 Mutation bei HR+/HER2- nach Progress
- *PIK3CA* Mutation (Exon 9 und 20) scheint ein prädiktiver Marker für Alpelisib zu sein
- Das Nebenwirkungsspektrum bedarf besonderer Beachtung und Schulung

Offene Fragen:

Wann erfolgt die Testung (timing) ?

Welcher Test? PCR/NGS?

Ergebnisbeurteilung? (Welche PIK3CA-Mutation?)

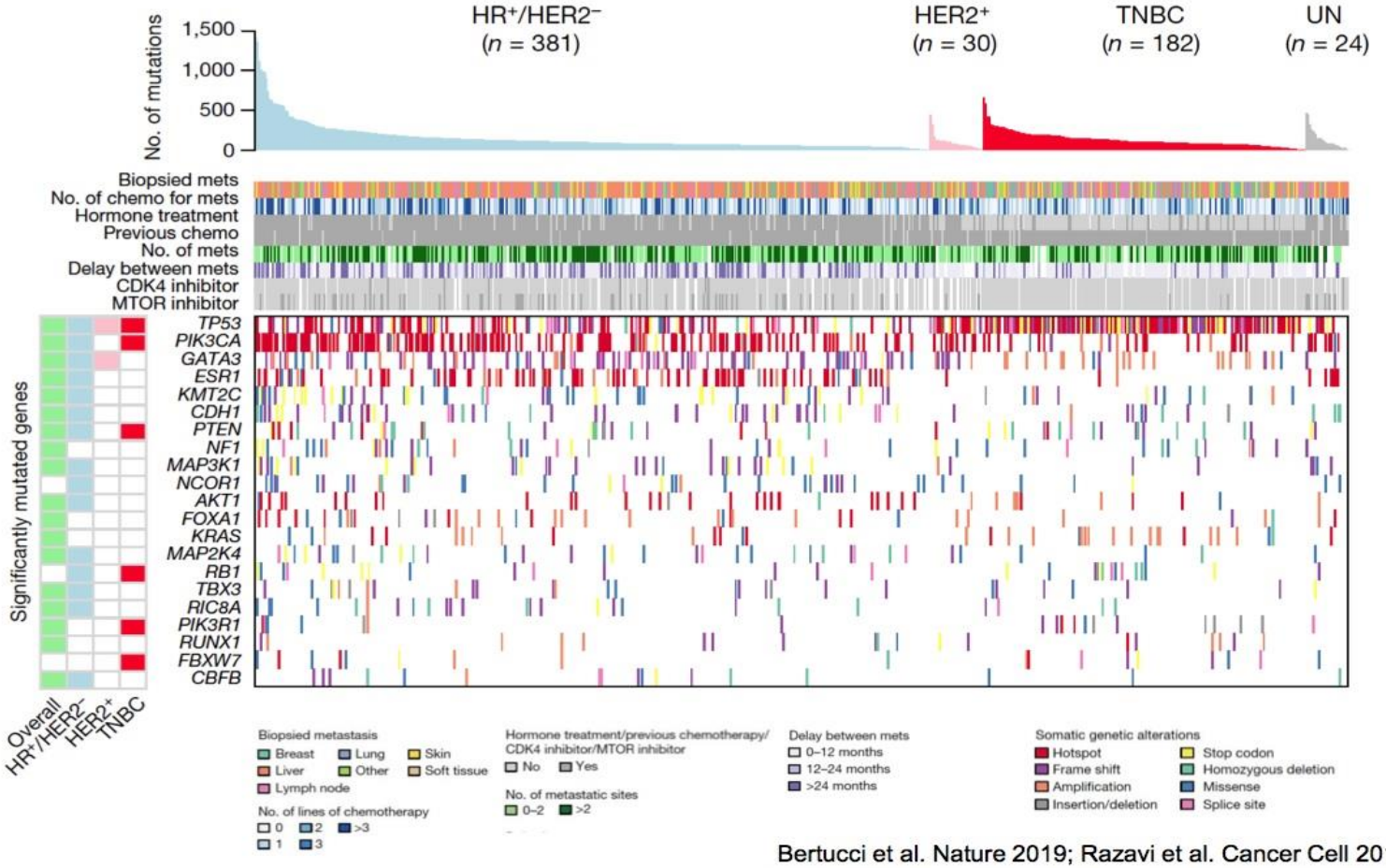
Testung an Gewebematerial oder Liquid Biopsie?

Stellenwert in der Therapiesequenz?

Zulassung mit Fulvestrant zu erwarten

Evolution der Metastasierung
TIMING?

Metastatic breast cancers differ from primary breast cancers (Whole-exome sequencing analysis of >600 metastatic cases)

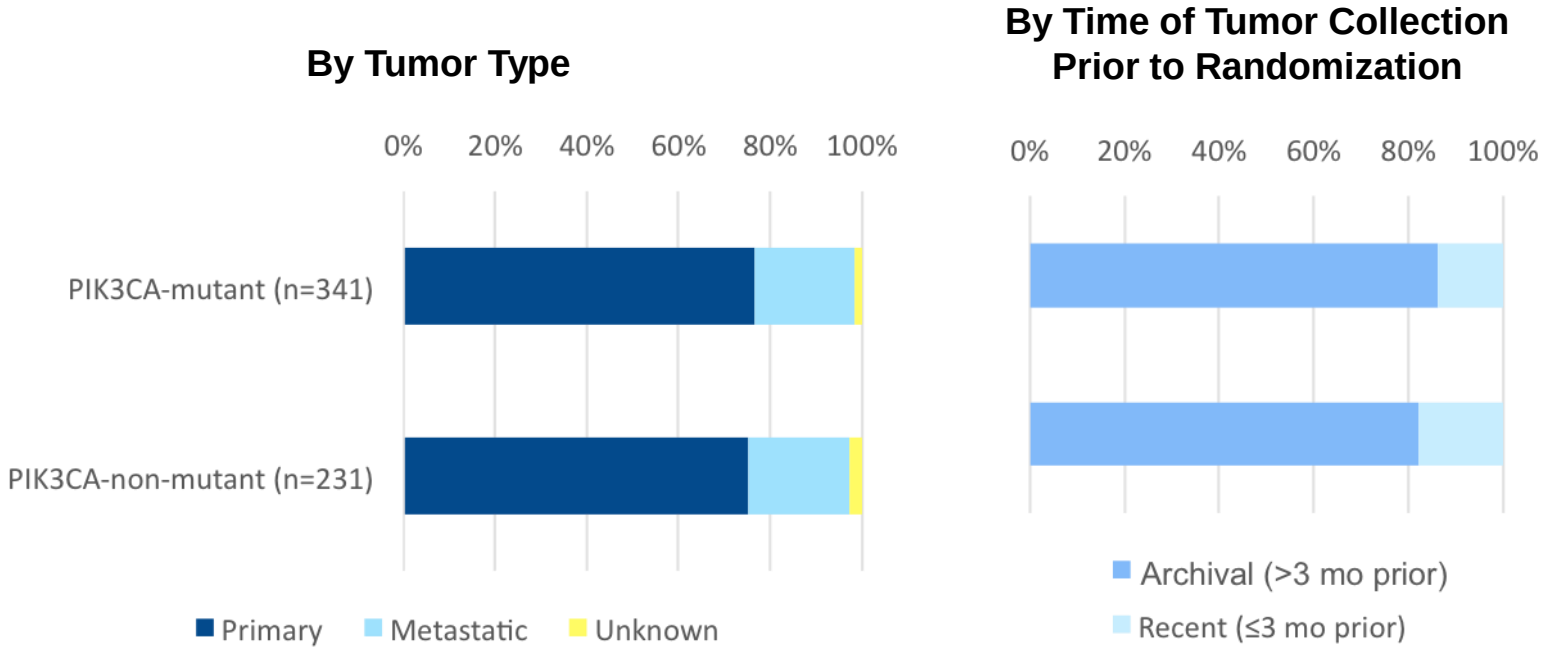


Bertucci et al. Nature 2019; Razavi et al. Cancer Cell 2018

TIMING?

Sample Type and Time of Collection for Patients in SOLAR-1

Die PIK3 CA Mutation ist vermutlich nicht durch Vorbehandlung beeinflusst oder erworben



- Majority of tissue samples used for *PIK3CA* screening at enrollment in SOLAR-1 were from primary tumors (vs metastatic sites)

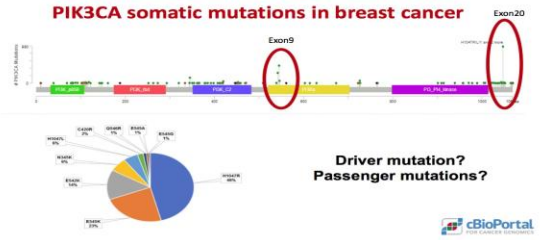
Freshly collected (≤3 months prior to randomization) vs archival (>3 months prior to randomization).
PCR, Polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Rugo HS, et al. AACR 2019. Abstract CT142 [poster].

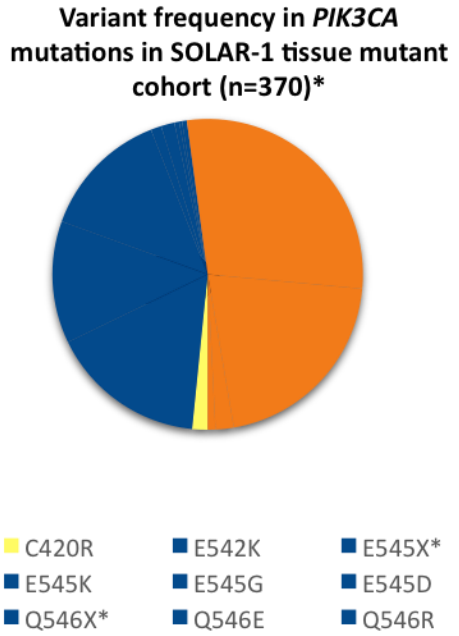
Testergebnisbeurteilung

Most Frequent Mutations Found in the Helical Domain (exon 9) and Kinase Domain (exon 20) by PCR in SOLAR-1

Exon	Mutation	SOLAR-1 tissue mutant cohort[a] N=370 (%)
7	C420R	6 (1.6)
9	**E542K**	**60 (16.2)**
	E545X[b] (A/D/G/K)	**47 (12.7)**
	E545K	**50 (13.5)**
	E545G	4 (1.1)
	E545D	5 (1.4)
	Q546X[b] (E/K/R)	2 (0.5)
	Q546E	1 (0.3)
	Q546R	2 (0.5)
20	**H1047X[b] (L/R/Y)**	**106 (28.6)**
	H1047R	**77 (20.8)**
	H1047L	7 (1.9)
	H1047Y	3 (0.8)

PCR, Polymerase chain reaction; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
[a] One patient may have ≥1 mutations detected by PCR assay.
[b] The Novartis clinical trial assay did not differentiate all mutations and reported E545X for E545A/D/G/K mutations, Q546X for Q546E/K/R mutations, and H1047X for H1047L/R/Y mutations. Due to prevalence H1047X will predominantly be comprised of H1047R mutations, and E545X will predominantly be comprised of E545K mutations.
Rugo HS, et al. AACR 2019. Abstract CT142 [poster].





- Of the 341 patients whose tumors were *PIK3CA* mutant per PCR at screening, 28 (8%) had multiple mutations
  - 370 mutations were detected in these 341 patients

Wichtige Aspekte

- ***PIK3CA* mutation** ist die **häufigste Mutation** des HR + Mammakarzinoms

- ***PIK3CA* mutationen** kommen in verschiedenen Lokalisationen vor, zudem gibt es eine Anzahl seltener Mutationen
  - Klinische Signifikanz der **seltenen Mutationen** unklar
  - NGS Untersuchungen können begleitende Mutationen nachweisen, deren klinische Signifikanz unklar ist

- ***PIK3CA* mutationen** können **im Gewebe** und in der **liquid-Biopsie** nachgewiesen werden
  - **Liquid biopsies** sollten zum **Zeitpunkt des Progresses** durchgeführt werden
  - Negative Ergebnisse der liquid biopsies müssen nicht durch eine Gewebeuntersuchung bestätigt werden

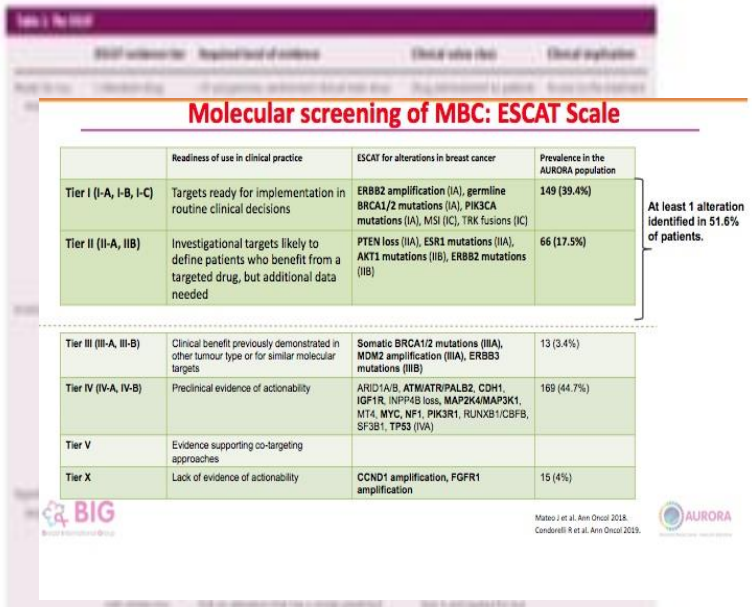
ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Publication of ESCAT in Annals of Oncology

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12,13] & L. Pusztai[14]

Mateo et al, Ann Oncol. 2018 Sep 1;29(9):1895-1902.
doi: 10.1093/annonc/mdy263.



Molecular screening of MBC: ESCAT Scale

	Readiness of use in clinical practice	ESCAT for alterations in breast cancer	Prevalence in the AURORA population
Tier I (I-A, I-B, I-C)	Targets ready for implementation in routine clinical decisions	**ERBB2 amplification** (IA), **germline BRCA1/2 mutations** (IA), **PIK3CA mutations** (IA), MSI (IC), TRK fusions (IC)	**149 (39.4%)**
Tier II (II-A, IIB)	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	**PTEN loss** (IIA), **ESR1 mutations** (IIA), **AKT1 mutations** (IIB), **ERBB2 mutations** (IIB)	**66 (17.5%)**
Tier III (III-A, III-B)	Clinical benefit previously demonstrated in other tumour type or for similar molecular targets	**Somatic BRCA1/2 mutations (IIIA), MDM2 amplification (IIIA), ERBB3 mutations (IIIB)**	13 (3.4%)
Tier IV (IV-A, IV-B)	Preclinical evidence of actionability	ARID1A/B, **ATM/ATR/PALB2**, **CDH1**, **IGF1R**, INPP4B loss, **MAP2K4/MAP3K1**, MT4, **MYC**, **NF1**, **PIK3R1**, RUNXB1/CBFB, SF3B1, **TP53** (IVA)	169 (44.7%)
Tier V	Evidence supporting co-targeting approaches		
Tier X	Lack of evidence of actionability	**CCND1 amplification, FGFR1 amplification**	15 (4%)

At least 1 alteration identified in 51.6% of patients.

BIG

Mateo J et al. Ann Oncol 2018.
Condorelli R et al. Ann Oncol 2019.

AURORA

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier II

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Investigational	II: Alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown	II-A: Retrospective studies show patients with the specific **PTEN loss in TNBC, ESR1 mutations** experience clinically meaningful benefit with matched drug compared to alteration-negative patients II-B: Prospective clinical trial(s) show the alteration-drug match **AKT1 & ERBB2 mutations in breast cancers** treated with a match drug, however no data currently available on survival endpoints.	Drug administered to a molecularly defined population is likely to result in clinical benefit in a given tumor type, but additional data is needed	**Treatment to be considered preferable in the context of evidence collection either as a prospective registry or as a prospective clinical trial**

HR POSITIVE / HER-2 NEGATIVE MBC

Abstimmungsergebnis 2017 +2019 beim ABC

- Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, <u>even in the presence of visceral disease</u>, unless there is visceral crisis or concern/proof of endocrine resistance. (LoE: 1 A)

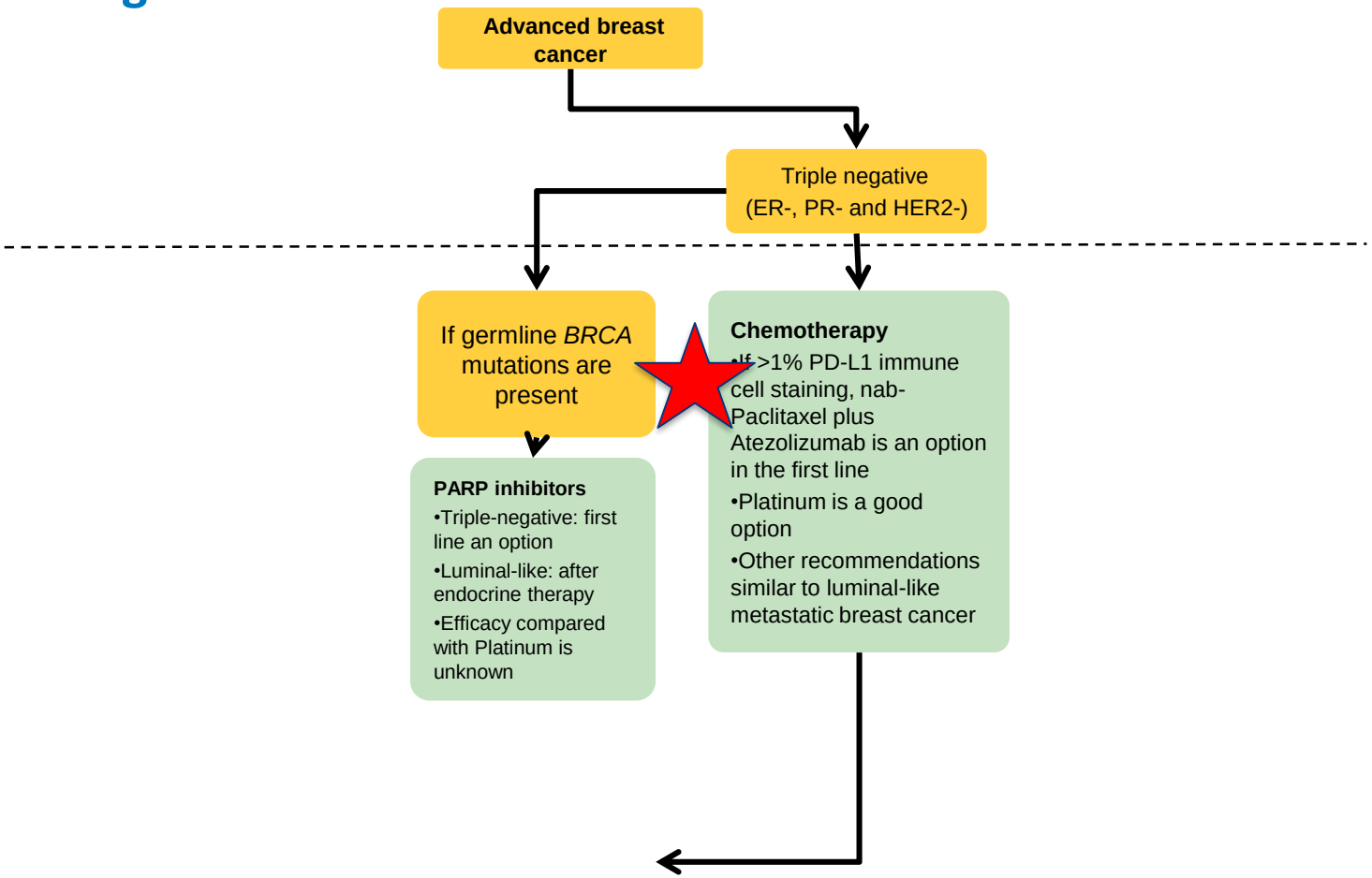
Total # of votes	(41)	(35)
[redacted]	92.6% (38)	97,1%(34)
	0.0% (0)	2,8% (1)
	7.3% (3)	0.0%(0)

ABC 5 2019

Mod. Cardoso F et al. Ann Oncol 2017. 28(1):16-33

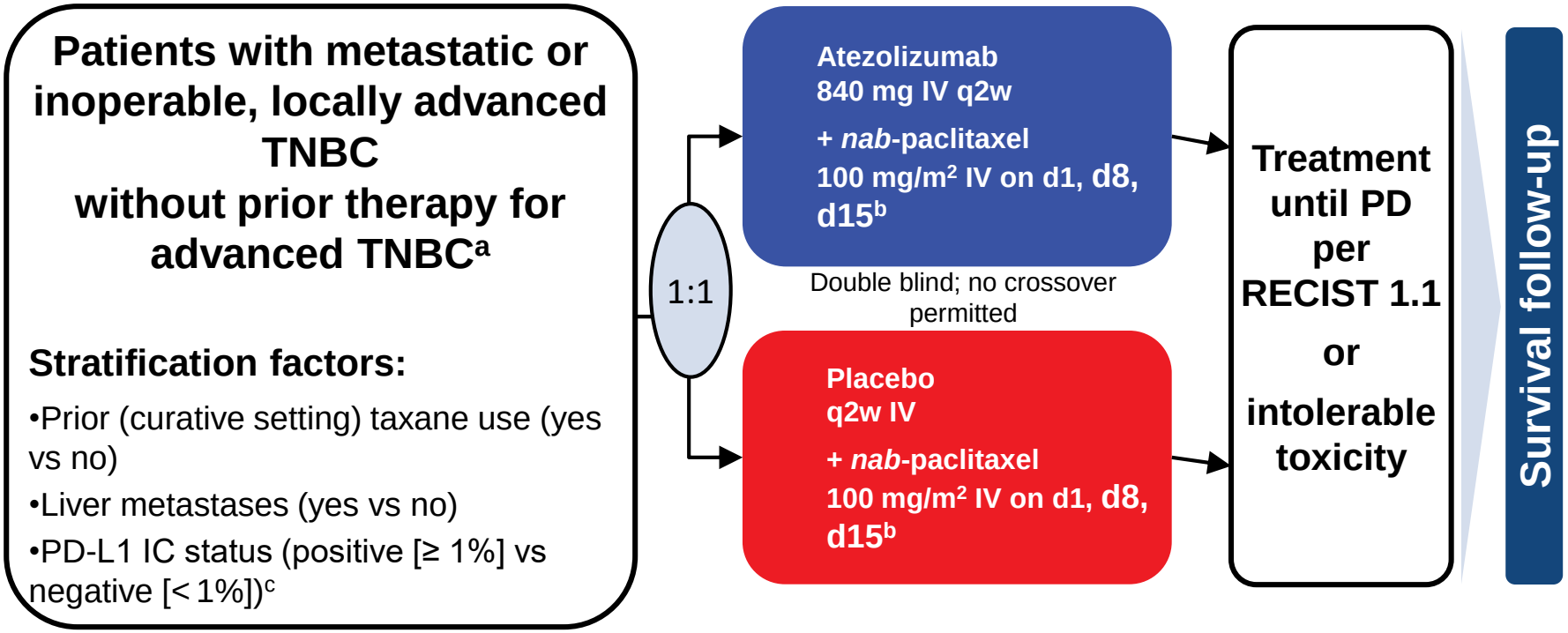
Metastatic breast cancer

Treatment strategies



Mod. Harbeck N et al., Nat Rev Dis Primers 9/2019;5(1):66

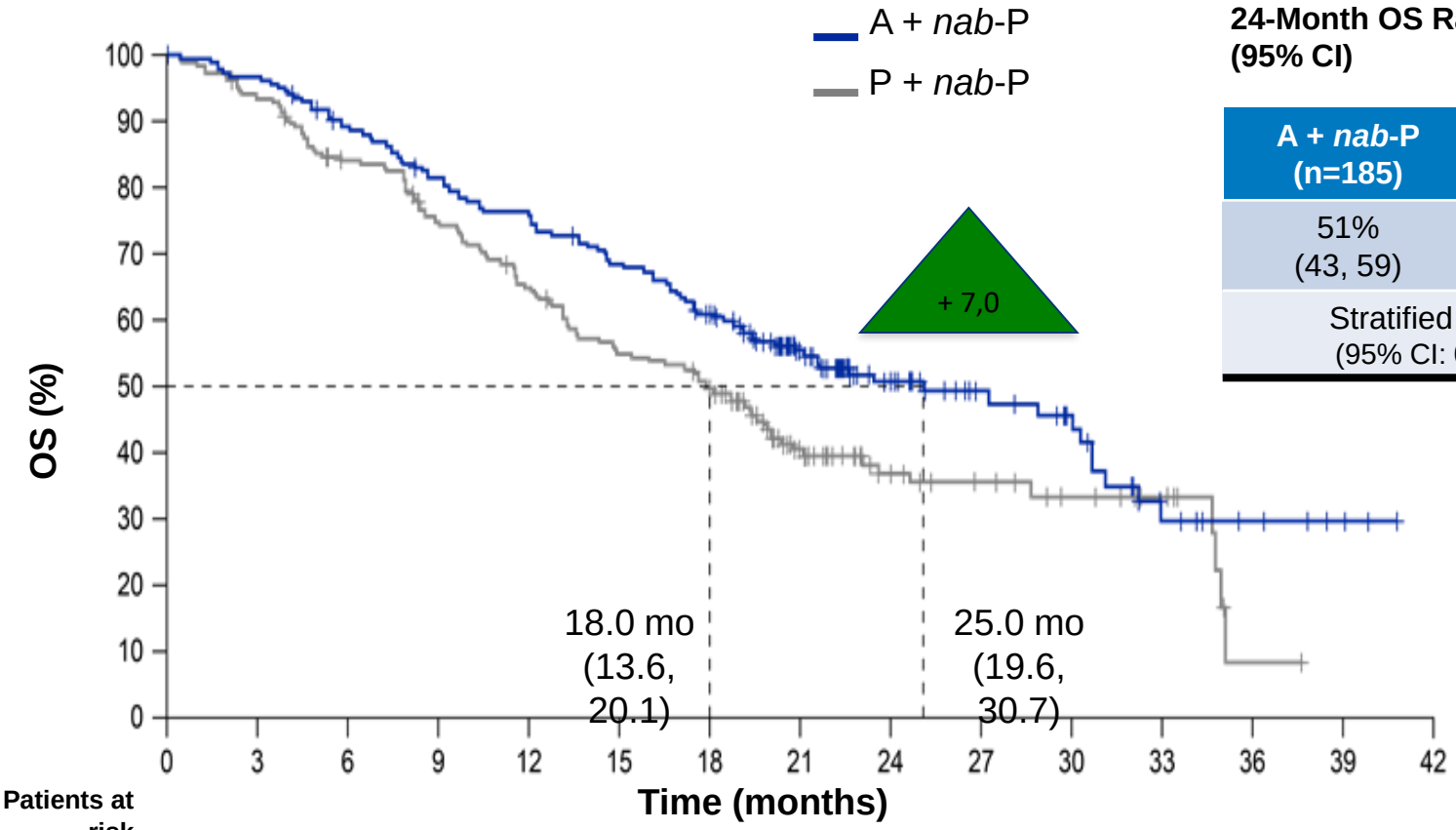
IMpassion130 Study Design



- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

IMpassion130
OS in PD-L1+ Population



24-Month OS Rate (95% CI)

A + *nab*-P (n=185)	P + *nab*-P (n=184)
51% (43, 59)	37% (29, 45)
Stratified HR, 0.71[a] (95% CI: 0.54, 0.93)	

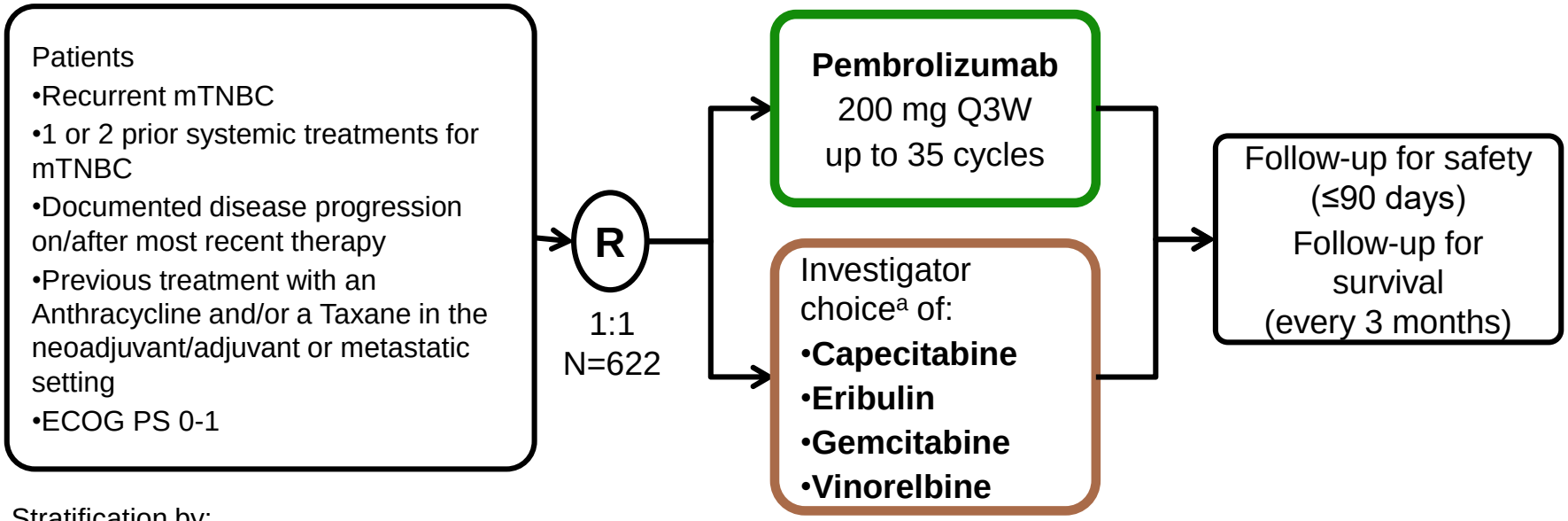
Patients at risk															
	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
A + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE
P + *nab*-P															

[a]Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months..

Mod. Schmid P et al. ASCO 2019, Oral Abstract Session – Breast Cancer – Metastatic, Abstract No. 1003

KEYNOTE-119 – Study Design



Stratification by:

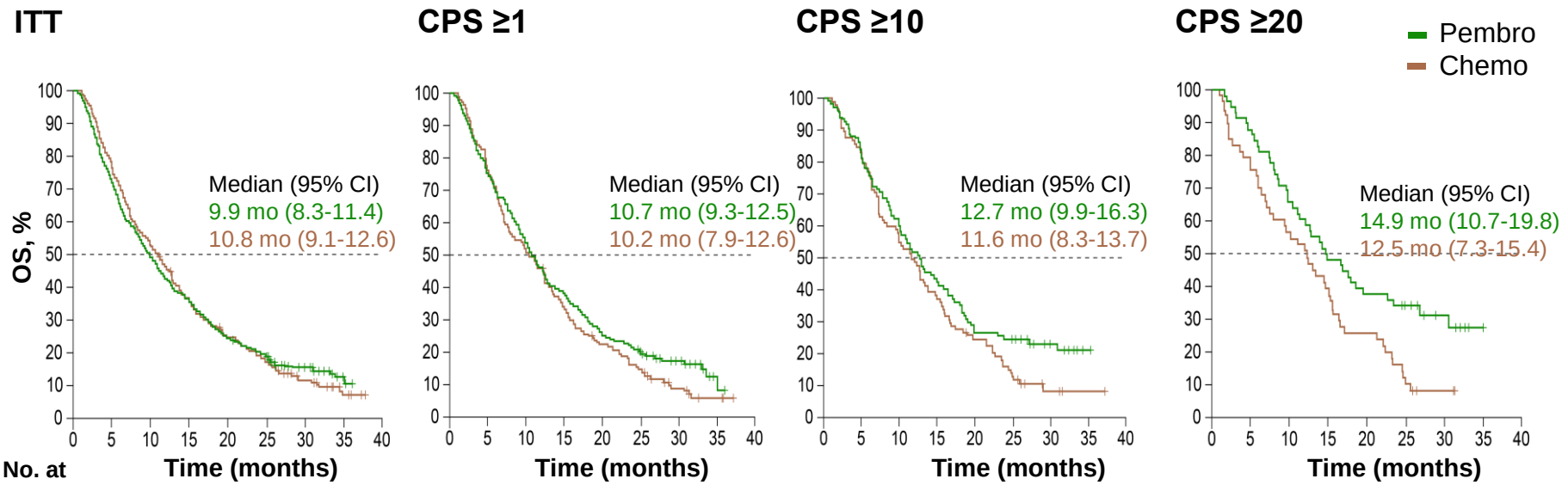
- PD-L1 tumor status (CPS ≥1 vs. CPS <1)
- Prior neoadjuvant/adjuvant therapy vs. de novo metastatic disease at initial diagnosis

ECOG PS, Eastern Cooperative Oncology Group performance status; mTNBC, metastatic triple-negative breast cancer; PD-L1, programmed death ligand 1; Q3W, every 3 weeks

[a]Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug

Mod. Cortés J et al. ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Abstract No. LBA21

KEYNOTE-119 – Overall Survival by PD-L1 CPS



No. at Risk

Pembro	3	2	1	1	7	5	3	6	0
Chemo	2	2	5	1	6	7	1	6	0
	3	4	4	2	7	4	2		
	1	2	1	1	5	8	1		
	0	3	6	0					
		3	3	8					

Pembro	2	1	1	7	5	4	2	3	0
Chemo	0	5	0	6	1	0	0	3	0
	3	1	9	6	4	2	1		
	2	5	1	6	2	7	2		
	0	2	0						
	2	2	2						

Pembro	9	7	5	4	2	2	1	1	0
Chemo	6	9	7	1	6	3	1	1	0
	9	8	5	3	2	1	4		
	8	0	4	6	3	2			

Pembro	5	5	3	2	2	1	8	1	0
Chemo	7	0	9	8	1	8	2	0	0
	5	4	2	2	3	6			
	2	1	9	0					

	Events	HR (95%CI)
Pembro	85.3%	0.97 (0.82-1.15)
Chemo	88.1%	

	Events	HR (95%CI)	p
Pembro	84.2%	0.86 (0.69-1.06)	0.073
Chemo	90.6%		

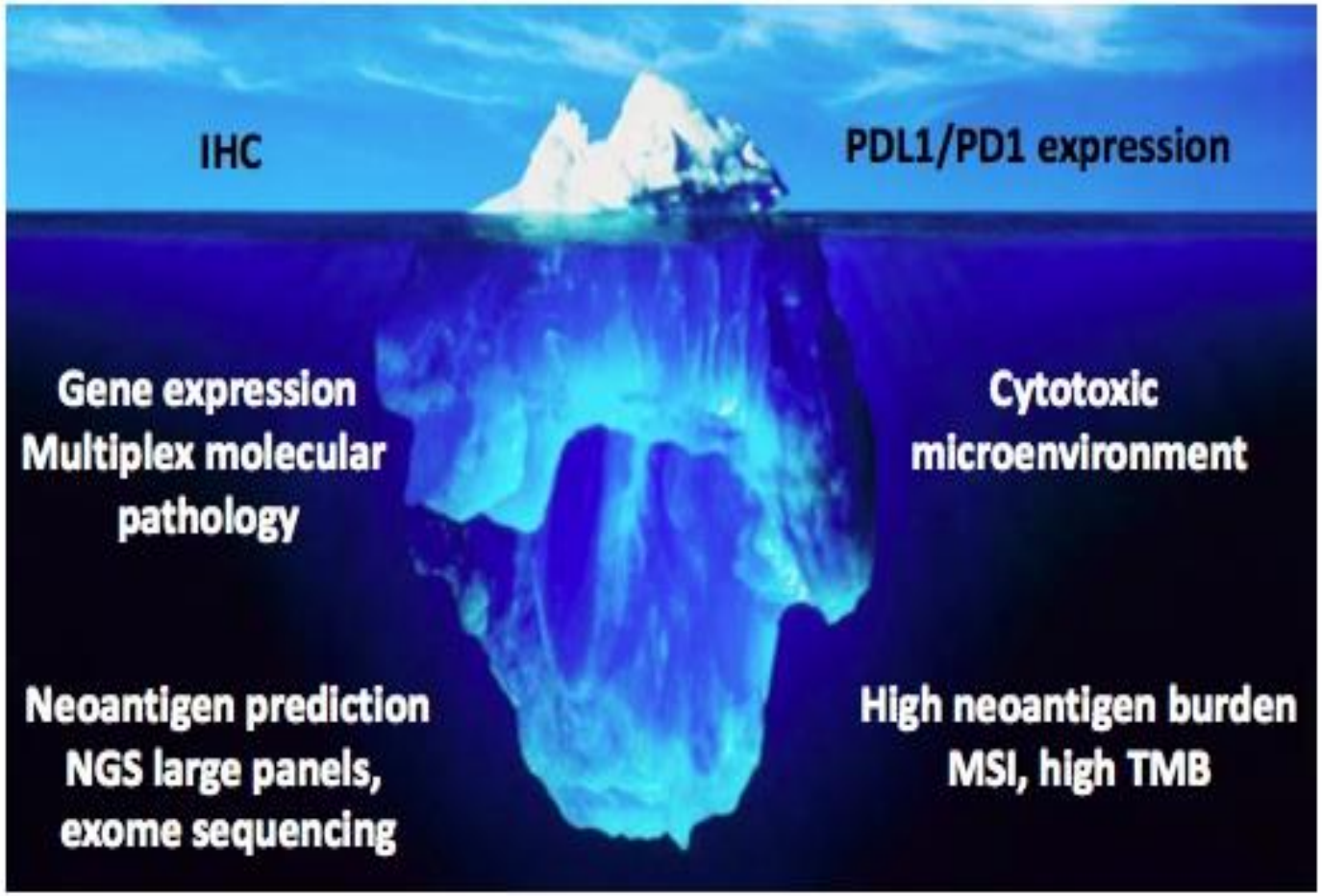
	Events	HR (95%CI)	p
Pembro	77.1%	0.78 (0.57-1.06)	0.057
Chemo	88.8%		

	Events	HR (95%CI)
Pembro	70.2%	0.58 (0.38-0.88)
Chemo	92.3%	

OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint
Data cutoff date: April 11, 2019

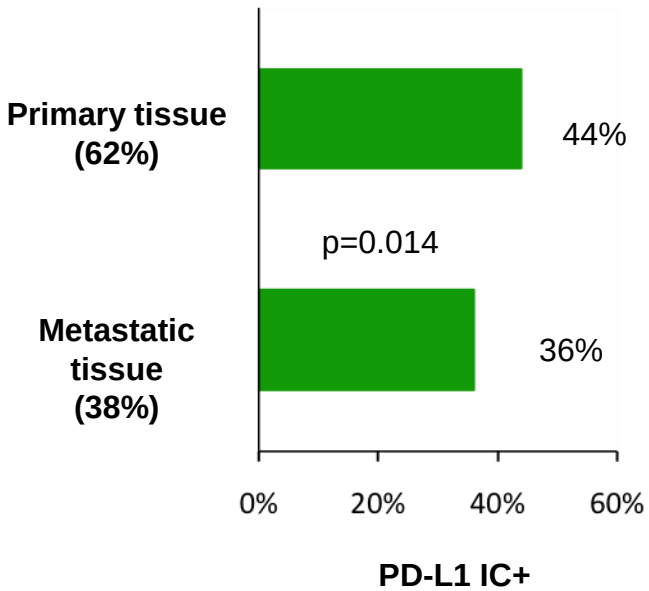
Mod. Cortés J et al. ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Abstract No. LBA21

INTEGRATED BIOMARKER ANALYSIS

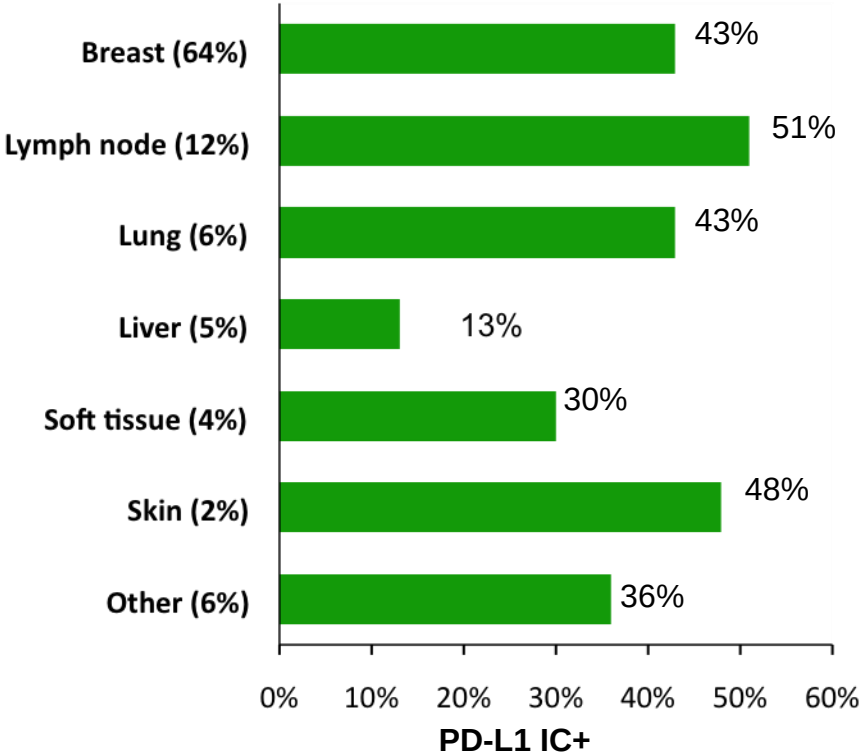


IMpassion130 – PD-L1 status in primary vs. metastatic tissues

PD-L1 status by primary vs. metastatic tissue[a]



PD-L1 status by anatomical location[a]

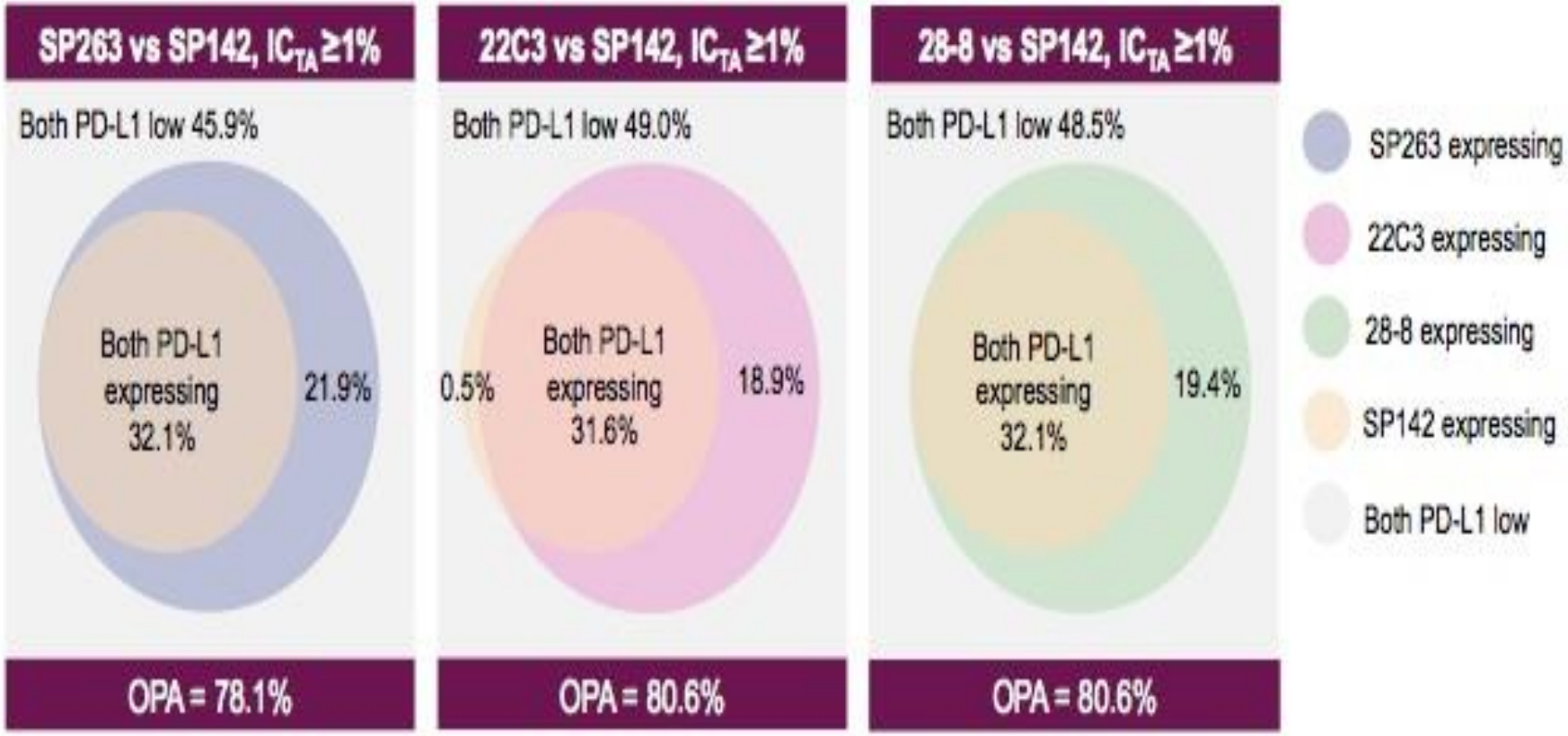


[a]Evaluable population (n=901). PD-L1 IC+: PD-L1 in ≥1% of IC as percentage of tumour area assessed with the VENTANA SP142 assay. HRs adjusted for prior taxanes, presence of liver metastases, age and ECOG PS. Median time of sample collection to randomization: 61 days. No major differences were observed for clinical benefit in samples collected within 61 days of randomization or beyond that period (Emens et al, manuscript in preparation)

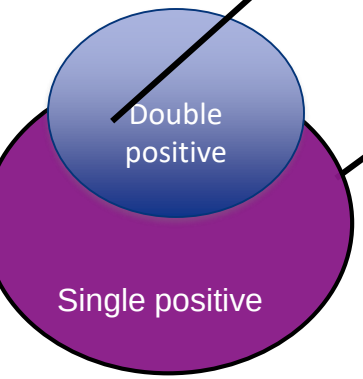
Mod. Rugo HS et al. ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Abstract No. LBA20

RESULTS

SP142 identifies ~20% fewer PD-L1 expressing patients at $IC_{TA} \geq 1\%$ than SP263, 22C3, 28-8



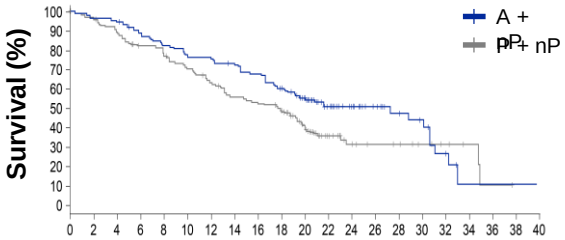
IMpassion130 – Clinical outcomes in BEP subpopulations defined by SP142 (IC 1%) and SP263 (IC 1%): OS



Double negatives

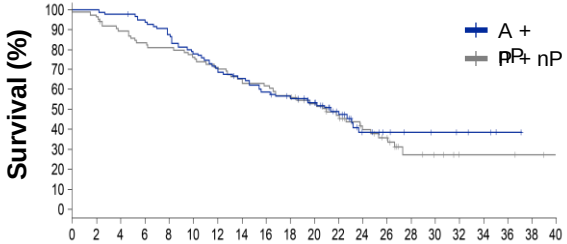
Population

SP142+ SP263+ (45%; 278/614)



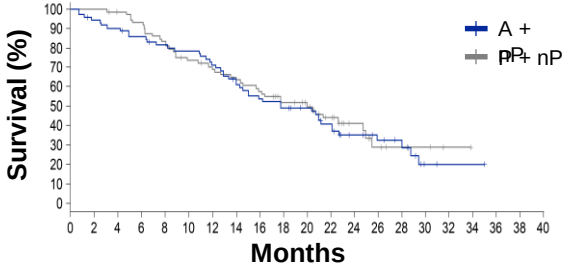
Median OS, mo			HR (95% CI)
A + nP	P + nP	Δ	
27.3	17.9	9.4	0.71 (0.52, 0.97)

SP142- SP263+ (30%; 182/614)



Median OS, mo			HR (95% CI)
A + nP	P + nP	Δ	
21.4	21.0	0.4	0.87 (0.58, 1.29)

SP142- SP263- (24%; 147/614)



Median OS, mo			HR (95% CI)
A + nP	P + nP	Δ	
17.9	20.5	-2.6	1.10 (0.72, 1.68)

Double positive: SP142 IC ≥1%, SP263 IC ≥1%; single positive: SP142 IC <1%, SP263 IC ≥1%; double negative: SP142 IC <1%, SP263 IC <1%
HR adjusted for prior Taxanes, presence of liver metastases, age and ECOG PS

Mod. Rugo HS et al. ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Abstract No. LBA20

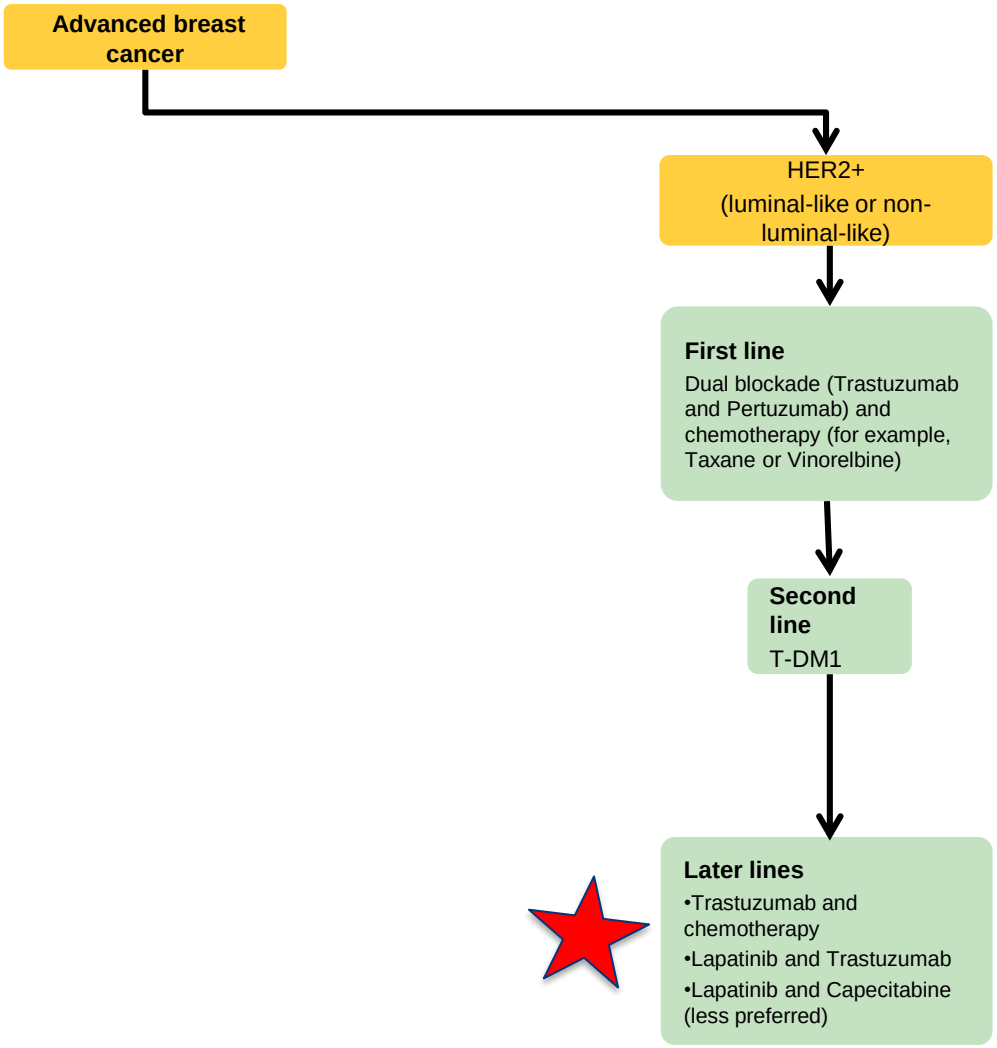
IMpassion130, KEYNOTE-119 – What have we learnt from these studies?

- Differently from other solid tumors, PD-L1 status in advanced TN breast cancer seems to identify distinct disease entities with different likelihood to benefit from immune checkpoints
- PD-L1 **assays are not easily interchangeable** (tell your pathologist what are you asking for)
- Studies with “one size fits all” approach should be avoided
- PD-L1 negative tumors may need different immunotherapy approaches or alternative therapeutic strategies
- The **benefit in PD-L1+ is still restricted to a minority**. New studies and approaches with IO are needed
- Effective biomarkers are urgently needed towards precision immunology

Mod. Bianchini G ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Discussion Abstract No. LBA20, LBA21 and 305O

Metastatic breast cancer

Treatment strategies



Mod. Harbeck N et al., Nat Rev Dis Primers 9/2019;5(1):66

Treatment pathways bei HER2+ MBC

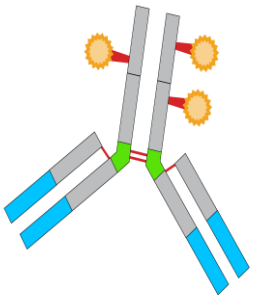
Cardoso CH et al. Ann Oncol 2018;29:1634–57 and NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, ver 2.2018

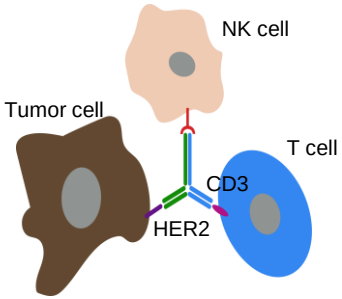
	Standard approach	Options
First Line	Taxane + Trastuzumab + Pertuzumab	T-DM1 (if adjuvant Trastuzumab-free interval <6 months)
Second Line	T-DM-1	Dual blockade if not given earlier
>2nd Line	Capecitabine + Lapatinib Chemotherapy + Trastuzumab Lapatinib + Trastuzumab For HR positive: ER + HER2 targeted therapy	Dual blockade or T-DM1 if not given earlier

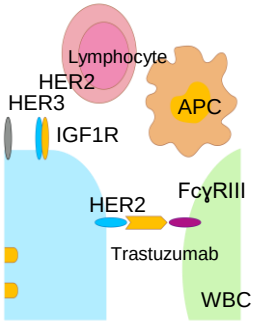
Keine etablierten Strategien in der 3. oder höheren Linie

Neue HER2-zielgerichtete Therapien

Class	Drugs (selection)
Tyrosine kinase inhibitors	Pyrotinib (pan HER2), **Tucatinib** (HER2), Neratinib (HER1, 2, 4), Poziotinib (pan HER)
Drug conjugates	**Trastuzumab Deruxtecan** (Exatecan derivate) SYD985 (Duocarmycin)
Bispecific antibodies	MCLA-128 (HER2/HER3) ZW25 (two different HER2 epitopes)
Modified antibodies	**Margetuximab** (Fc-optimized Ab for ADCC)







Tong et al. Front Oncol 2018; Yu et al. Exp Hematol Oncol 2017

monarcHER – Study Design

Eligibility Criteria

- HR+, HER2+ ABC
- ≥2 prior HER2 directed therapies for ABC
- Prior T-DM1 and Taxane required
- CDK4 & 6 inhibitor/ Fulvestrant naive
- No untreated or symptomatic CNS metastases

Stratification Factors

•Number of previous systemic regimens (2–3 vs. >3)

•Measurable vs. nonmeasurable

N=23

R

1:1:1

Sample Size Calculations

•165 PFS events give 80% power at 2-sided alpha of 0.20, assuming a HR of 0.667

Continue until PD

Arm A
Abemaciclib 150 mg PO BID +
Trastuzumab IV q21d
+
Fulvestrant[a] IM q28d

Arm B
Abemaciclib 150 mg PO BID +
Trastuzumab IV q21d

Arm C
Trastuzumab IV q21d
+
investigator's choice chemotherapy[b]

Primary Endpoint

•PFS[c] (A vs. C, then B vs. C)

Secondary Endpoint

•ORR, safety, OS, PRO, PK

ABC, advanced breast cancer, HR+, hormone receptor-positive; HER2(+), human epidermal growth factor receptor-2 (positive), n, number of patients; PD, progressive disease
BID, twice daily; q21d, every 21 days; PFS, Progression Free Survival; ORR, Objective Response Rate; OS, Overall Survival; PRO, Patient Reported Outcomes, PK, pharmacokinetics
[a]Dosing per Fulvestrant label; [b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer; [c]investigator assessed

Mod. Tolaney SM et al. ESMO 2019, Proffered Paper Session – Breast cancer, metastatic, Abstract No. LBA23

monarcHER STUDY DESIGN

Eligibility Criteria
- HR+, HER2+ ABC
- ≥2 prior HER2 directed therapies for ABC
- prior T-DM1 and taxane required
- CDK4 & 6 inhibitor/ fulvestrant naive
- No untreated or symptomatic CNS metastases

Stratification Factors:
- number of previous systemic regimens (2–3 vs. >3)
- measurable vs. nonmeasurable

Randomization
N = 237
1:1:1

Sample Size Calculations:
- 165 PFS events give 80% power at 2-sided alpha of 0.20, assuming a HR of 0.667

Continue until PD

Arm A
abemaciclib 150 mg PO BID + trastuzumab IV q21d + fulvestrant[a] IM q28d

Arm B
abemaciclib 150 mg PO BID + trastuzumab IV q21d

Arm C
trastuzumab IV q21d + investigator's choice chemotherapy[b]

Primary Endpoint
- PFS[c] (A vs. C, then B vs. C)

Secondary Endpoint
- ORR, safety, OS, PRO, PK

BARCELONA 2019 ESMO congress

Abbreviations: ABC = adv
progressive disease, BID=
Outcomes, PK = pharmac
[a]Dosing per fulvestrant la
[b]Standard-of-care single-
[c]Investigator assessed

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

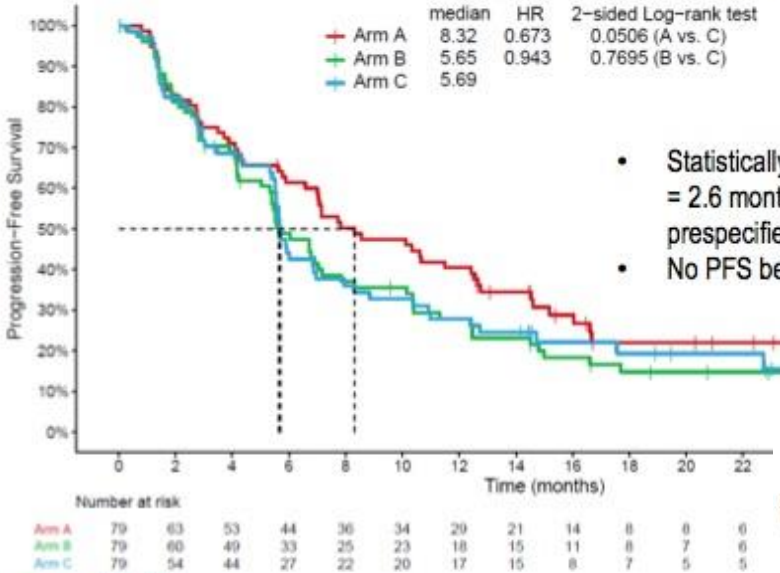
	Arm A N=79	Arm B N=79	Arm C[b] N=79
Median age, years (range)	55 (31-78)	54 (28-83)	57 (29-82)
Geographic distribution, n (%)			
Asia / Pacific	13 (16.5)	13 (16.5)	12 (15.2)
Europe	30 (38.0)	45 (57.0)	36 (45.6)
N. America	24 (30.4)	13 (16.5)	24 (30.4)
S. America	12 (15.2)	8 (10.1)	7 (8.9)
Metastatic Site, n (%)			
Visceral	58 (73.4)	56 (70.9)	48 (60.8)
Bone-only	7 (8.9)	3 (3.8)	7 (8.9)
Measurable disease, n (%)	70 (88.6)	68 (86.1)	69 (87.3)
Prior systemic therapies for ABC, n (%)			
2 to 3	35 (44.3)	44 (55.7)	40 (50.6)
More than 3	44 (55.7)	35 (44.3)	39 (49.4)
Prior endocrine therapy overall[a], n (%)	63 (79.7)	60 (75.9)	60 (75.9)
Tamoxifen in any setting	35 (44.3)	45 (57.0)	37 (46.8)
AI in any setting	46 (58.2)	42 (53.2)	42 (53.2)
Prior HER2 therapies for ABC, n (%)			
trastuzumab	77 (97.5)	76 (96.2)	79 (100.0)
trastuzumab emtansine	77 (97.5)	78 (98.7)	77 (97.5)
pertuzumab	43 (54.4)	37 (46.8)	39 (49.4)
lapatinib	35 (44.3)	37 (46.8)	31 (39.2)

BARCELONA 2019 ESMO congress

[a]any of the following: letrozole, anastrozole, exemestane, tamoxifen
[b]most common chemotherapy: Vinorelbine (37.5%) , Capecitabine (26.4%) , Eribulin (16.7%), Gemcitabine (11.1%)

PRIMARY ENDPOINT: PFS

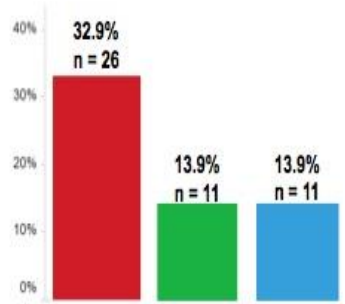
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

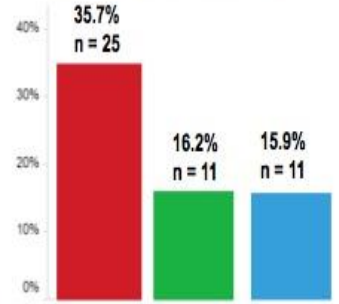
CONFIRMED BEST OVERALL RESPONSE RATE

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached



Measurable Disease
Total N = 207

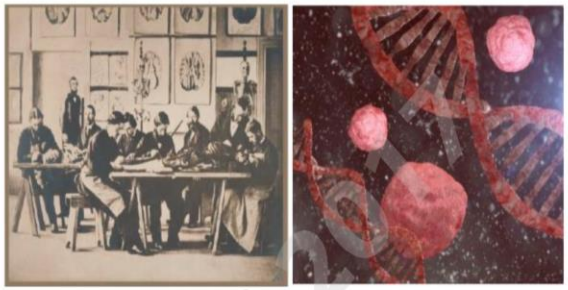
	Arm A N=70	Arm B N=68	Arm C N=69
95% CI (%)	(24.5-46.9)	(7.4-24.9)	(7.3-24.6)
Stratified 2-sided p-value (vs Arm C)	0.0111	1.0000	-
Duration of Response, months	10.4	9.5	not reached

The future.....

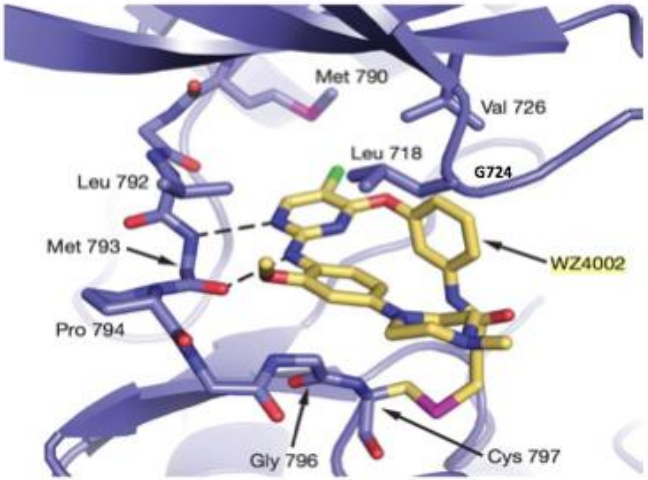
San Antonio Breast Cancer Symposium, December 5-9, 2017

What can the blood tell us?

- 1869: Thomas Ashworth
- Observed cells in the blood that were identical to the cancer itself
- 1948: Mandel & Metais observed cell free DNA in the blood
- 1977: Leon et. al. showed higher levels of cfDNA in cancer patients



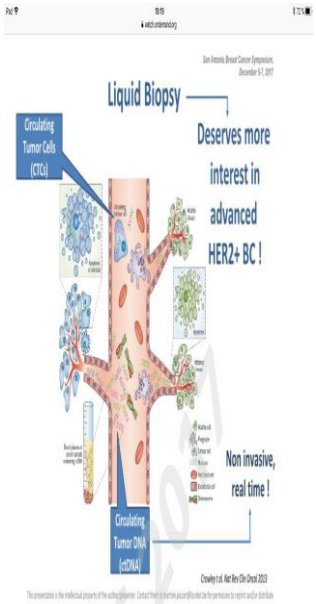
Overcoming resistance by structure-based compound design



Zhou et al., Nature 2009

San Antonio Breast Cancer Symposium, December 5-9, 2017

Characteristics of ctDNA



Crowley et al. Nat Rev Clin Oncol 2013

LOKALE THERAPIE IM PALLIATIVEN SETTING
....“zurück zur Erde“

Lokale Therapie des Primarius in der metastasierten de novo Situation

Locoregional therapy targeted at the primary tumour improves overall survival in patients presenting with de novo stage IV metastatic breast cancer: A systematic review and meta-analysis of real-world data with 201598 patients

Salim Tayeh, Ritika Gera, Hiba El Hage Chehade, Umar Wazir, Abdul Kasem and Kefah Mokbel.
The London Breast Institute, Princess Grace Hospital, London, United Kingdom

ABSTRACT

Background:
De novo stage IV metastatic breast cancer is a complex disease that is traditionally treated using systemic therapy. There is mounting evidence that locoregional therapy (LRT), defined as resection of the primary tumour and/or localised radiotherapy, could be associated with survival improvements. We aimed to conduct a meta-analysis to inform decision making.

Methods:
Using the PubMed, Cochrane and Ovid SP databases, a literature review and meta-analysis was undertaken to assess whether LRT of the primary tumour in metastatic breast cancer prolongs survival.

Results:
48 studies met the criteria for analysing the efficacy of all locoregional treatments (radiotherapy and/or surgery) and 44 studies were suitable for the analysis of surgery-only treatment of the primary. Studies were analysed for the impact of LRT on survival. All LRT resulted in a significant 32.9% reduction in mortality with LRT (N=48; HR=0.671: 95% CI 0.624-0.721). Primary resection alone resulted in a significant 36.9% mortality (N=44; HR=0.631: 95% CI 0.591-0.674).

Conclusions:
This is the largest meta-analysis regarding this question to date. LRT seems to improve overall survival in stage IV disease at initial diagnosis and should be considered in selected patients after a multidisciplinary discussion.

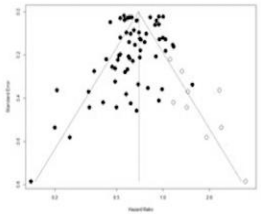
INTRODUCTION

De novo metastatic breast cancer has poor prognosis in affected patients and is commonly treated with palliative intent. However, the aim of this study was to determine whether locoregional surgery and/or irradiation of the breast could improve overall survival. We assessed combination locoregional therapy and surgical resection of the breast to determine the extent to which radiotherapy additionally influences overall survival outcomes. This is an update of a previously published meta-analysis by Mokbel et al (2016)[1], where analysis of sixteen studies resulted in the observation of a 37% mortality reduction associated with surgical resection of the primary tumour. We used a random effects model of statistical analysis to generate forest plots and also assessed for bias in included studies.

METHODS

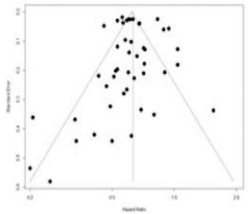
The PubMed, Cochrane, and Ovid SP databases were searched to find studies which were prospective clinical trials and retrospective studies examining adult patients diagnosed with histologically confirmed stage IV breast cancer and distant metastases. The study must have reported overall survival outcomes and 95% confidence intervals (CIs) of patients who had undergone surgical resection, radiotherapy, or no treatment of the primary tumour. Conservative and extended resections were also considered. Studies were excluded from the meta-analysis if: there was a failure to report hazard ratios (HRs) and 95% CIs for overall survival, the full text was not available for data extraction, and they were reviews/case reports/letters/commentaries. Cochran's Q test, $\chi 2$ test, and the I^2 statistic were used to assess and quantify statistical heterogeneity and the random effects model was used to report the overall HR.

RESULTS



Result 1: Funnel plot with Duval and Tweedie's trim and fill method to assess for bias in studies included in combined LRT of the breast vs no treatment analysis. There are a relatively large number of studies outside the 95% CI, indicating significant heterogeneity between reported results. **Duval and Tweedie's trim and fill suggests that 8 studies should be imputed to correct for asymmetry,** which are represented on the funnel plot using unpainted dots.

However, tests using Begg and Mazumdar Rank Correlation and Egger's calculations do not provide evidence for asymmetry or publication bias **(Begg and Mazumdar Rank Correlation Test, P=0.3007; Egger's test, P=0.6263)**. The Classic fail-safe N test (Rosenberg method) suggests that **as many as 48312 studies would be required to reduce the significance level of the pooled effect size to 5%.** Hence, **effect sizes were significant even in view of some publication bias.**



Result 2: Funnel plot with Duval and Tweedie's trim and fill method to assess for bias in studies included in surgery of the breast alone vs no treatment analysis. Although there are a relatively large number of studies outside the 95% CI, indicating significant heterogeneity between reported results, **Duval and Tweedie's trim and fill suggests that 0 studies need to be imputed** to correct for asymmetry.

Furthermore, tests using Begg and Mazumdar Rank Correlation and Egger's calculations do not provide evidence for asymmetry or publication bias **(Begg and Mazumdar Rank Correlation Test, P=0.2255; Egger's test, P=0.9120)**. The Classic fail-safe N test (Rosenberg method) suggests that **as many as 41173 studies would be required to reduce the significance level of the pooled effect size to 5%.** Hence, **effect sizes were significant even in view of some publication bias.**

RESULTS

Combined LRT of the breast results in a 32.9% risk reduction in mortality and surgery of the breast alone alone results in a 36.9% risk reduction in patients; both findings are highly significant. Patients with HER2/ER positive disease confined to the bone benefited more from LRT compared to patients with extensive visceral metastases and/or triple negative disease. Patients who respond well to systemic therapy derive greater benefit from LRT. Resectability of the tumor is also an important factor to take into consideration.

DISCUSSION

The underlying mechanisms that can explain our observations are most likely multifactorial and are likely related to the: removal of mammary circulating tumour cells (CTCs) within the primary tumour[2], interruption of the self-seeding process[3], and immunomodulation[4]. Although we found no evidence of publication bias, the selection bias of patients represents an important limitation in the studies included. We speculate that surgery alone shows a greater risk reduction because patients suffering from more aggressive disease, which is non-responsive to systemic therapy, are more likely to require breast irradiation along with/as an alternative to surgical resection. Prospective analyses from multiple clinical trials was not included due to their low accrual rate or paucity of data (NCT01906112, NCT01392586). As most of the data sets were retrospective, it is impossible to definitively state that no treatment to the axilla was administered.

CONCLUSIONS

LRT significantly improves overall survival of patients presenting with stage IV breast cancer at initial diagnosis. It should be considered in a multidisciplinary setting, particularly in patients with a good response to primary systemic therapy and a resectable tumor. Although the focus of this study was to examine the effect of LRT on the primary breast tumour, we recognize that surgery of non-primary sites is an important aspect of clinical care and it is unlikely that clinicians would operate on the breast in isolation. Greater investigation is required to determine the role of LRT in a palliative context. Another interesting avenue of future investigation would be to determine whether circulating tumour cells (CTCs) can be used to assess patient eligibility for LRT.

REFERENCES

1. Headon H, Wazir U, Kasem A, Mokbel K. Surgical treatment of the primary tumour improves the overall survival in patients with metastatic breast cancer: A systematic review and meta-analysis. Mol Clin Oncol 2016;4(5):863–7.
2. Li S, Li Q. Cancer stem cells and tumor metastasis. Int J Oncol 2014;44(6):1806–12.
3. Kim M-Y, Oskarsson T, Acharyya S, et al. Tumor Self-Seeding by Circulating Cancer Cells. Cell 2009;139(7):1315–26.
4. Janssen LME, Ramsay EE, Logsdon CD, Overwijk WW. The immune system in cancer metastasis: friend or foe? J Immunother Cancer 2017;5(1):79

Corresponding author: Kefahmokbel@hotmail.co.uk
This meta-analysis was kindly funded by grants donated from the Breast Cancer Hope Foundation (London, UK). The authors have no competing interests.

P2-17-02

Lokale Therapie des Primarius in der metastasierten de novo-Situation

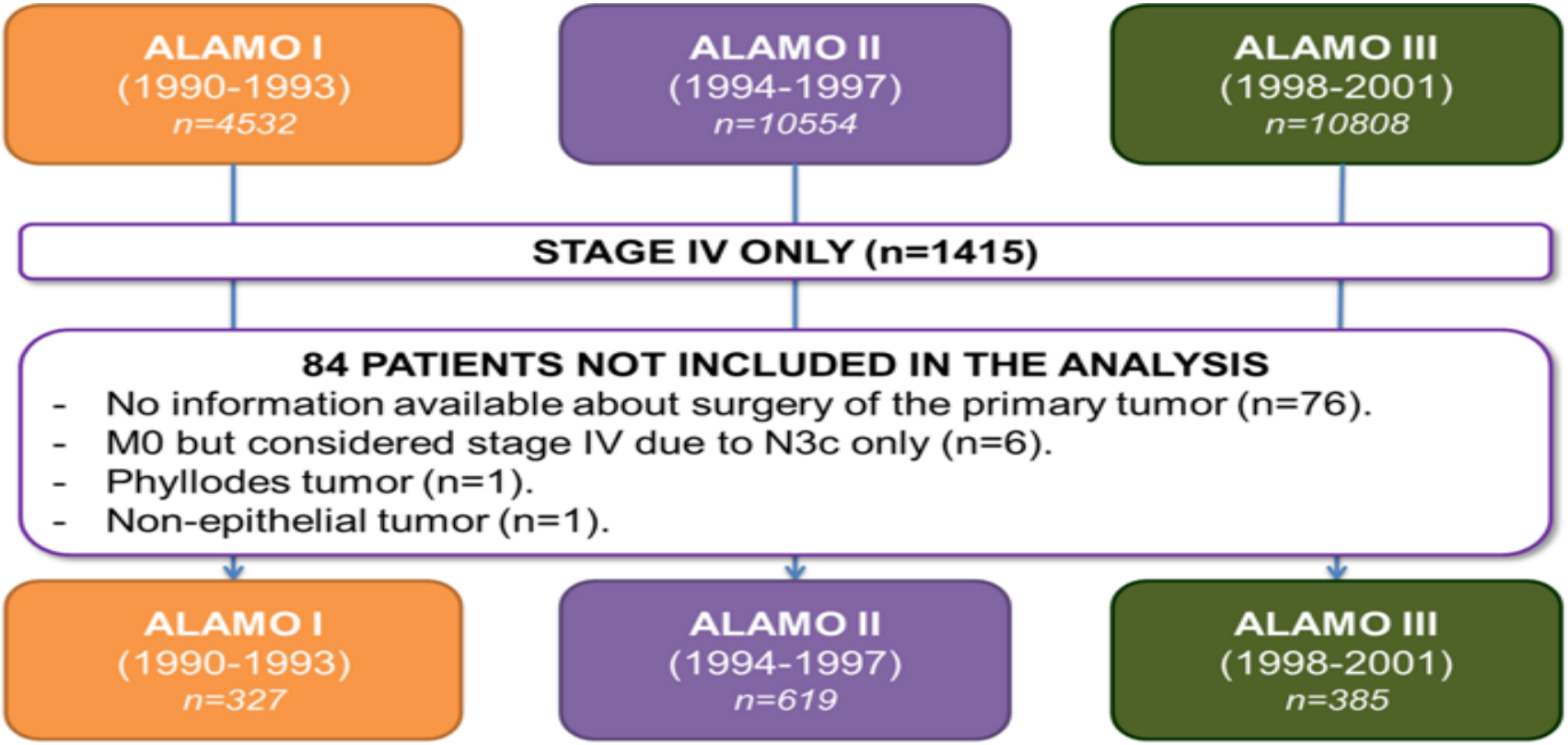
- Metaanalyse von überwiegend retrospektiven Studien (44/48), OS angaben verpflichtend
- Fokus: Nur OP versus OP und Bestrahlung
- Axilläre Interventionen unklar ob durchgeführt
- Grösster Vorteil bei HR+/HER2+, bei Pat mit gutem Ansprechen und resektablem Tumor

- Kombinierte LRT: 32,9% Risikoreduktion für Mortalität
- Nur OP: 36,9 % Risikored für Mortalität

Studien zur Rolle der LRT Therapie im palliativen setting weiter erforderlich!

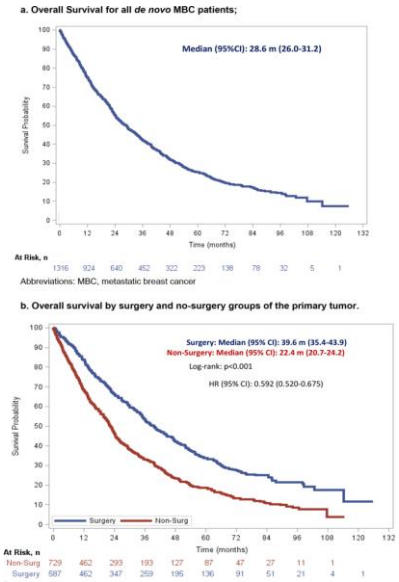
Lokale Therapie des Primarius in der metastasierten Situation

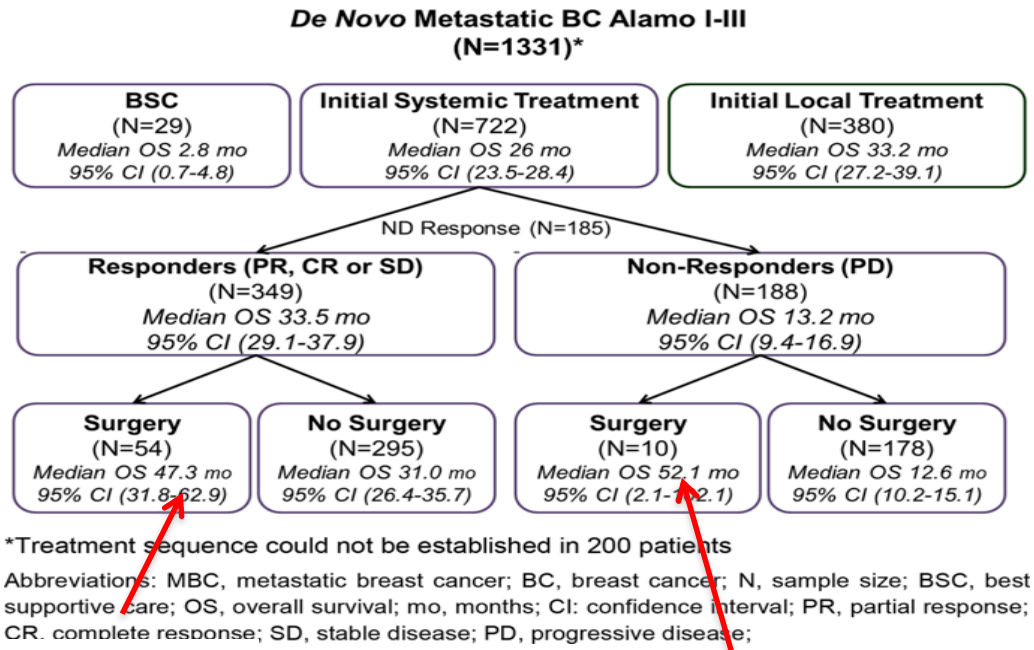
Retrospektive Analyse **Survival impact of primary tumor resection in de novo metastatic breast cancer patients (GeicAM/el Alamo Registry)**
Sara Lopez-tarruella
www.nature.com/scientificreports/
12/2019



Abbreviations: M, distant metastasis; N: node; n: sample size

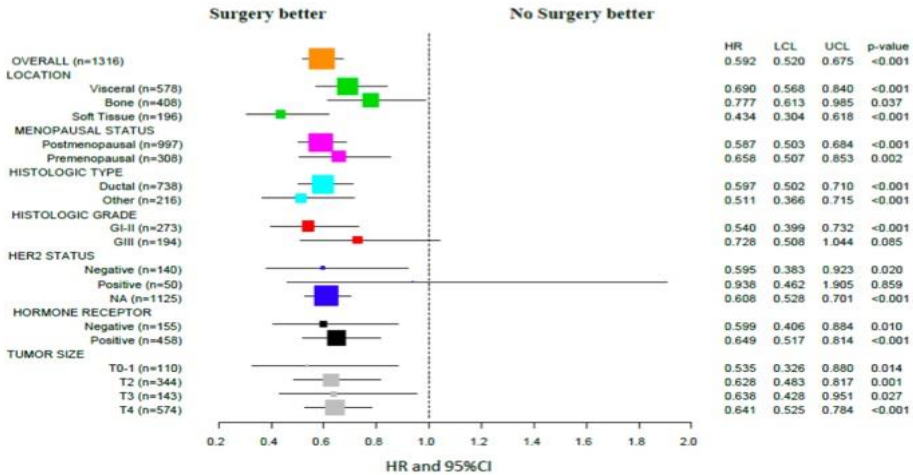
Lokale Therapie des Primarius in der metastasierten Situation





*Treatment sequence could not be established in 200 patients

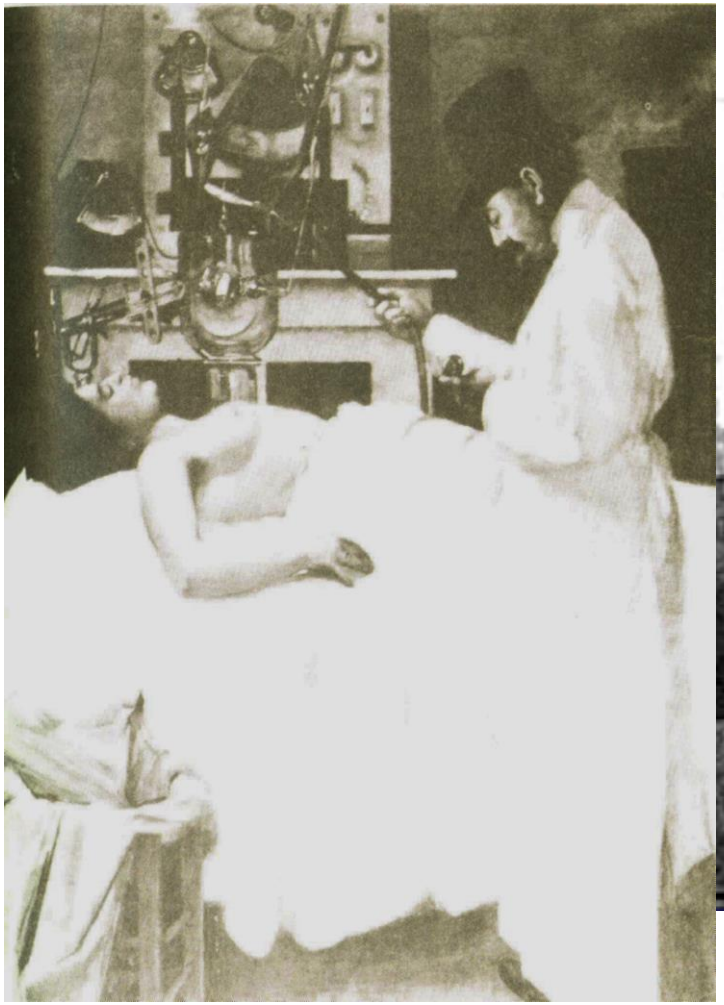
Abbreviations: MBC, metastatic breast cancer; BC, breast cancer; N, sample size; BSC, best supportive care; OS, overall survival; mo, months; CI: confidence interval; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease;



Abbreviations: G, grade; HER2, human epidermal growth factor receptor 2; NA, not-assessed; HR, Hazard ratio; LCL, lower confidence interval limit; UCL, upper confidence interval limit; T, tumor; CI, confidence interval.

Figure 4. Subgroup analysis of overall survival from *El Álamo* registry.

„Zurück zur Erde“
Danke für Ihre Aufmerksamkeit



- BACK UP

Guidelines Breast
Version 2019.1D

Endokrine Therapie des metastasierten Mammakarzinoms

Indikation

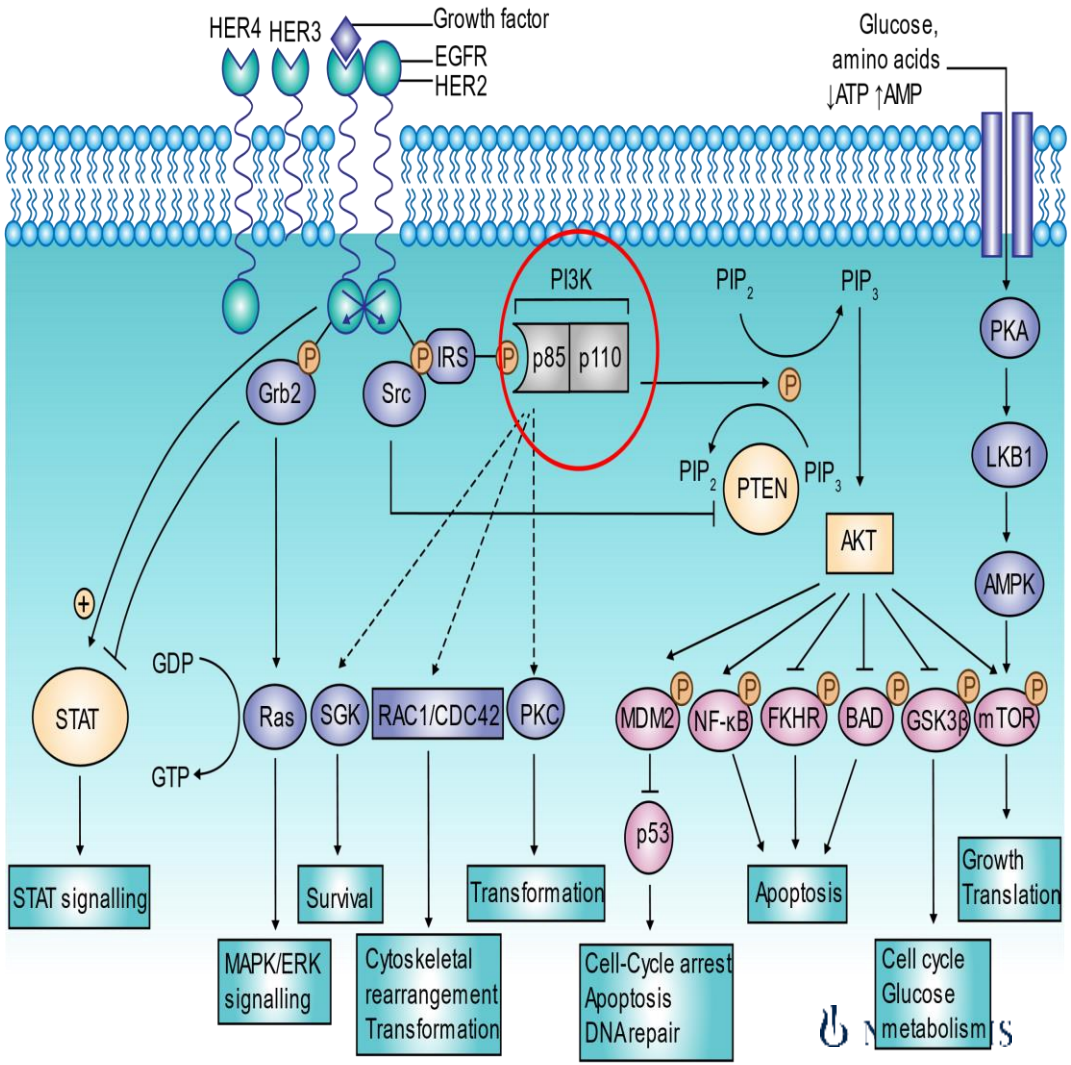
Oxford LoE: 1a **GR: A** **AGO: ++**

Die endokrin-basierte Therapie ist die erste Therapie-option in der Behandlung des metastasierten hormonrezeptor-positiven (oder -unbekannten) Mammakarzinoms

- **Ausnahme: drohender Organausfall**
- **Cave: Der HR-Status kann sich im Laufe der Er-krankung verändern. Falls möglich, sollte eine Histo-logie der neuen Metastase gewonnen werden**

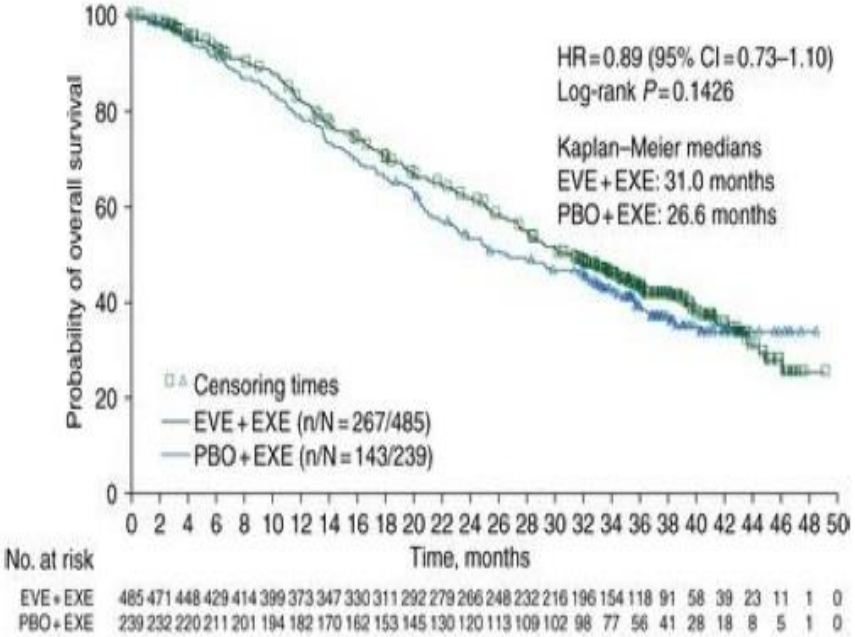
“We could be sure that any time our endocrine therapy falls”

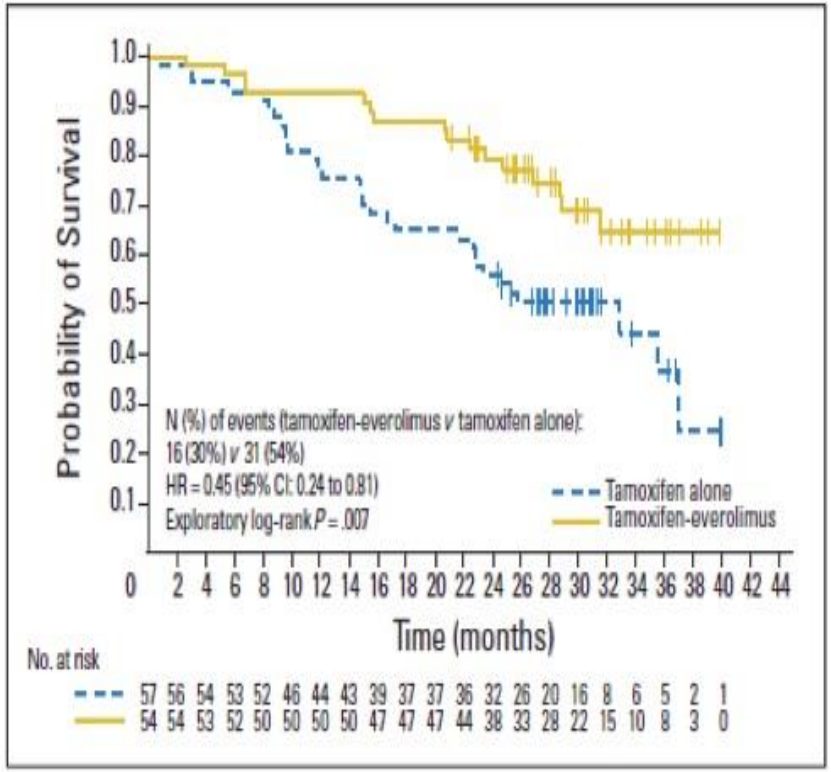
PI3K pathway alterations and the resulting hyperactivation contribute to malignant transformation and resistance to endocrine therapy[1-5]



1. Miller TW, et al. *J Clin Oncol*. 2011;29:4452-4461; 2. Saal LH, et al. *Proc Natl Acad Sci U S A.* 2007;104:7564-7569; 3. Hosford SR, Miller TW. *Pharmgenomics Pers Med.* 2014;7:203-215; 4. Shaw RJ & Cantley LC. *Nature.* 2006;441:424-430; 5. Reprinted from Hennessy BT, et al. *Nat Rev Drug Disc*. 2005;4:988-1004.

Overall Survival BOLERO-2 and TAMRAD





BARCELONA 2019 ESMO congress

Piccart M et al. New Engl J 2018; Bachelot T et al. J Clin Oncol 2012

Patient populations in PALOMA3, MONALEESA3 and MONARCH2

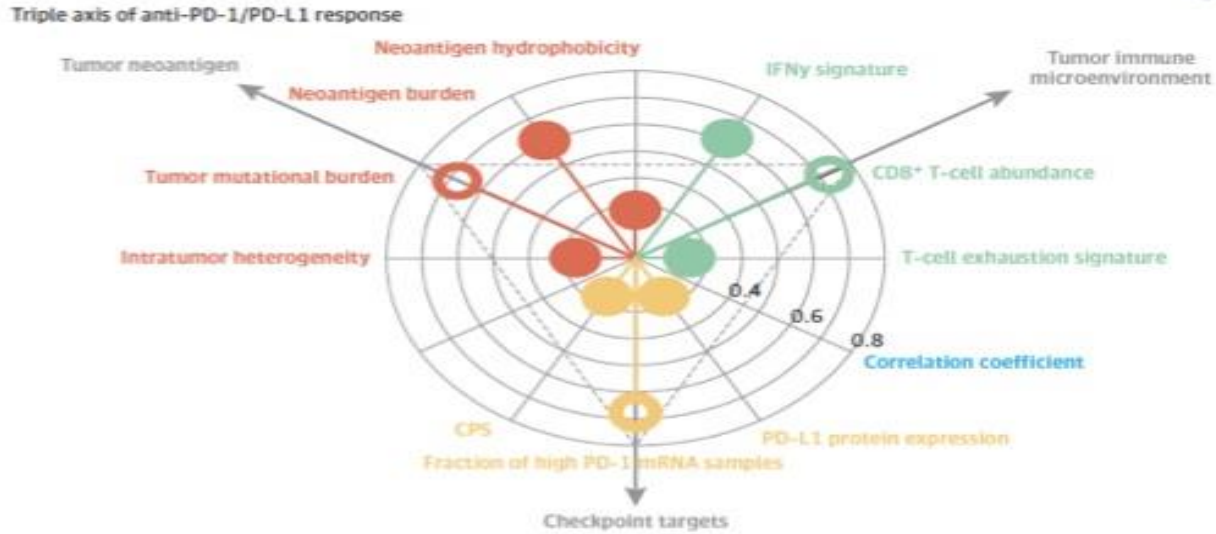
	PALOMA3[1] N=521		MONALEESA3[2] N=726		MONARCH2[3] N=669	
	Fulvestrant + palbociclib n (%)	Fulvestrant n (%)	Fulvestrant + ribociclib n (%)	Fulvestrant n (%)	Fulvestrant + abemaciclib n (%)	Fulvestrant n (%)
ET inclusion criteria	• **Progressed on or ≤12 months from prior adjuvant therapy with AI*/ tamoxifen** • **Progressed on or ≤1 month from prior advanced breast cancer with AI*/ ET**		• **First line (treatment naïve for ABC)** • **Second line + early relapsers**		• **Relapsed on neoadjuvant or on/within 1 year of adjuvant endocrine therapy** • **Progressed on first line therapy**	
Median age, years (range)	57 (30–88)	56 (29–80)	63 (31–89)	63 (34–86)	59 (32–91)	62 (32–87)
Most recent ET						
• **De novo†**	–	–	97 (20%)	42 (17.4%)	–	–
• **(neo)adjuvant setting**	74 (21%)*	40 (23%)*	289 (60%)	142 (59%)	263 (59%)	133 (60%)
• **ABC setting**	273 (79%)*	133 (76%)*	110 (23%)	40 (17%)	171 (38%)	85 (38%)
Prior chemotherapy	34% received 1 prior line of chemotherapy for ABC		No prior chemotherapy allowed in the advanced setting		No prior chemotherapy allowed in the advanced setting	
Postmenopausal at study entry - no. (%)	275 (79.3%)	138 (79.3%)	484 (100%)	242 (100%)	371 (83.2%)	1810 (80.7)
Visceral metastasis – no. (%)	206 (59.4%)	105 (60.3%)	293 (60.5%)	146 (60.3%)	245 (54.9%)	128 (57.4%)

BARCELONA 2019 ESMO congress

with courtesy adapted from Stephen Johnston

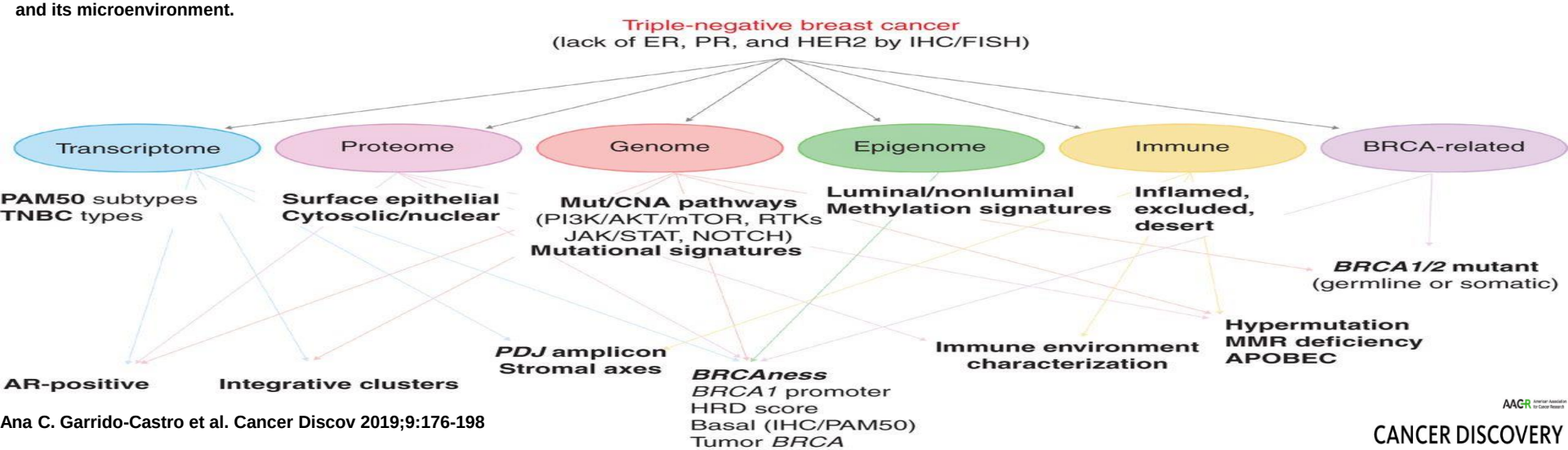
1. Cristofanilli M et al. *Lancet Oncol* 2016;17:425–39. 2. Slamon D et al. *J Clin Oncol* 2018;36:1–8; 3. Sledge GW et al. *J Clin Oncol* 2017;35:2875–2884.

MULTI-OMICS PREDICTIVE MARKERS



Lee & Ruppin, JAMA Oncol 2019

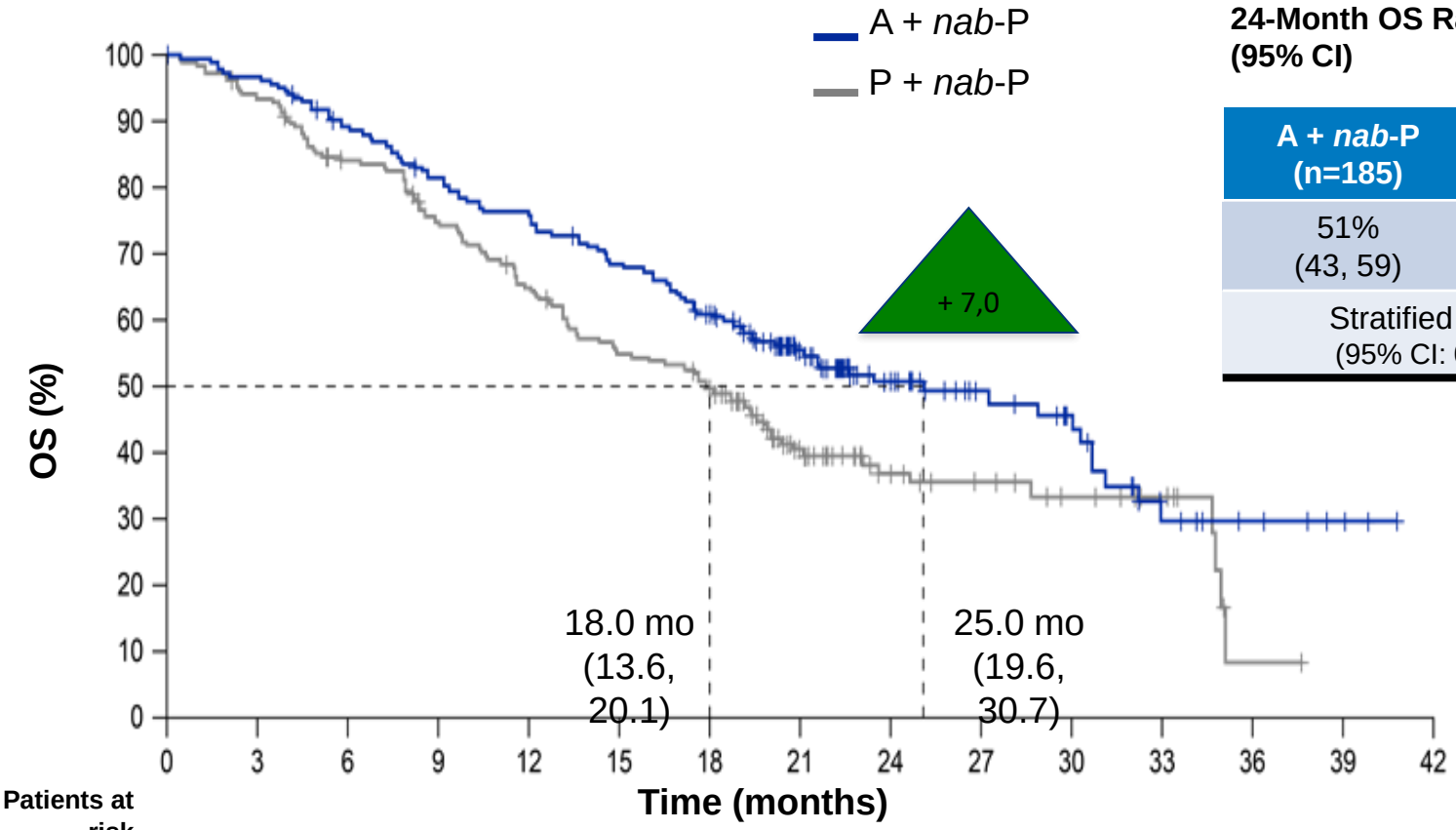
Overview of the complex interactions among molecular classifications of TNBC based on genomic, transcriptomic, proteomic, epigenomic, and immune characterization of the tumor and its microenvironment.



Ana C. Garrido-Castro et al. Cancer Discov 2019;9:176-198

CANCER DISCOVERY

IMpassion130
OS in PD-L1+ Population



24-Month OS Rate (95% CI)

A + *nab*-P (n=185)	P + *nab*-P (n=184)
51% (43, 59)	37% (29, 45)
Stratified HR, 0.71[a] (95% CI: 0.54, 0.93)	

Patients at risk															
	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
A + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE
P + *nab*-P															

[a]Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months..

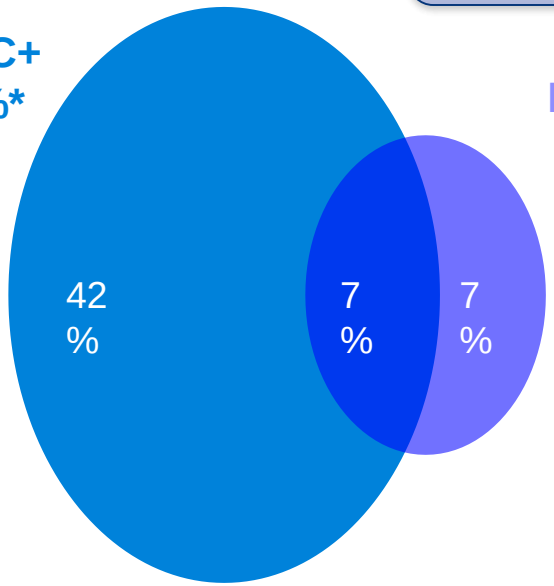
Mod. Schmid P et al. ASCO 2019, Oral Abstract Session – Breast Cancer – Metastatic, Abstract No. 1003

Patientinnen mit BRCA 1/2-mutierten Tumoren zeigten einen klinischen Benefit (PFS/OS) nur bei Tumoren PD-L1 IC+ !

Welche Therapiesequenz?
Diskussion spotlight Familiäres Mammakarzinom

PD-L1 IC+ 49 %*

***BRCA 1/2*-Mutation 15 %**



Keine *BRCA 1/2*-Mutation/PD-L1 IC+ (n = 257)

	HR (95 %-KI)	p-Wert
PFS	0,63 (0,48–0,83)	≤ 0,005
OS	0,62 (0,43–0,91)	0,01

***BRCA 1/2*-Mutation/PD-L1 IC– (n = 44)**

	HR (95 %-KI)	p-Wert
PFS	0,77 (0,37–1,61)	0,49
OS	0,85 (0,29–2,43)	0,76

***BRCA 1/2*-Mutation/PD-L1 IC+ (n = 45)**

	HR (95 %-KI)	p-Wert
PFS	0,45 (0,21–0,96)	0,04
OS	0,87 (0,26–2,85)	0,82

*bezogen auf Subgruppe mit BRCA-Testung

- *BRCA 1/2*-Mutationen und PD-L1-IC+ sind unabhängig voneinander (p = n. s.)*

TNBC: triple-negatives Mammakarzinom; PFS: Progressionsfreies Überleben; OS: Gesamtüberleben; PD-L1: programmed cell death-ligand 1; IC: tumorinfiltrierende Immunzellen

Auswertbare Population hinsichtlich *BRCA 1/2* (n = 612); *BRCA 1/2*-Mutationen: bekannte und anzunehmende Mutationen (anhand FoundationOne-Assay).
* Daten aus Kontingenztabelle abgeleitet mit dem exakten Fisher-Test. ** Dateninterpretation nur eingeschränkt möglich aufgrund der niedrigen Patientenzahlen mit *BRCA 1/2*-Mutationen.

IMpassion130 – NCT02425891; Mod. Emens LA et al. SABCS 2018.

Current treatment recommendations are based on 4 Key Phase III trials

	1st Line	2nd Line	3rd Line	>2nd Line
Trial	CLEOPATRA[1]	EMILIA[2]	TH3RESA[3]	EGF104900[4]
Number of pts	808	991	602	291
Treatment arms	Docetaxel + T + P vs. Docetaxel + T	T-DM1 vs. Capecitabine + L	T-DM1 vs. Physician's choice	TL vs. L
OS benefit	+ 16.3 months (40.8 vs. 57.1)	+ 4 months (25.9 vs. 29.9)	+ 6.9 months (15.8 vs. 22.7)	+ 4.5 months (9.5 vs. 14.0)
Side effects	Minimally increased	Less with T-DM1	Less with T-DM1	Minimally increased
Prior Trastuzumab	Only 10% and interval of ≥12 months required	100% (16% with adjuvant DFS <6 months)	Prior T&L	100% (≥3 regimen)